The American Journal of Medicine

October 1955

The American Journal of Medicine

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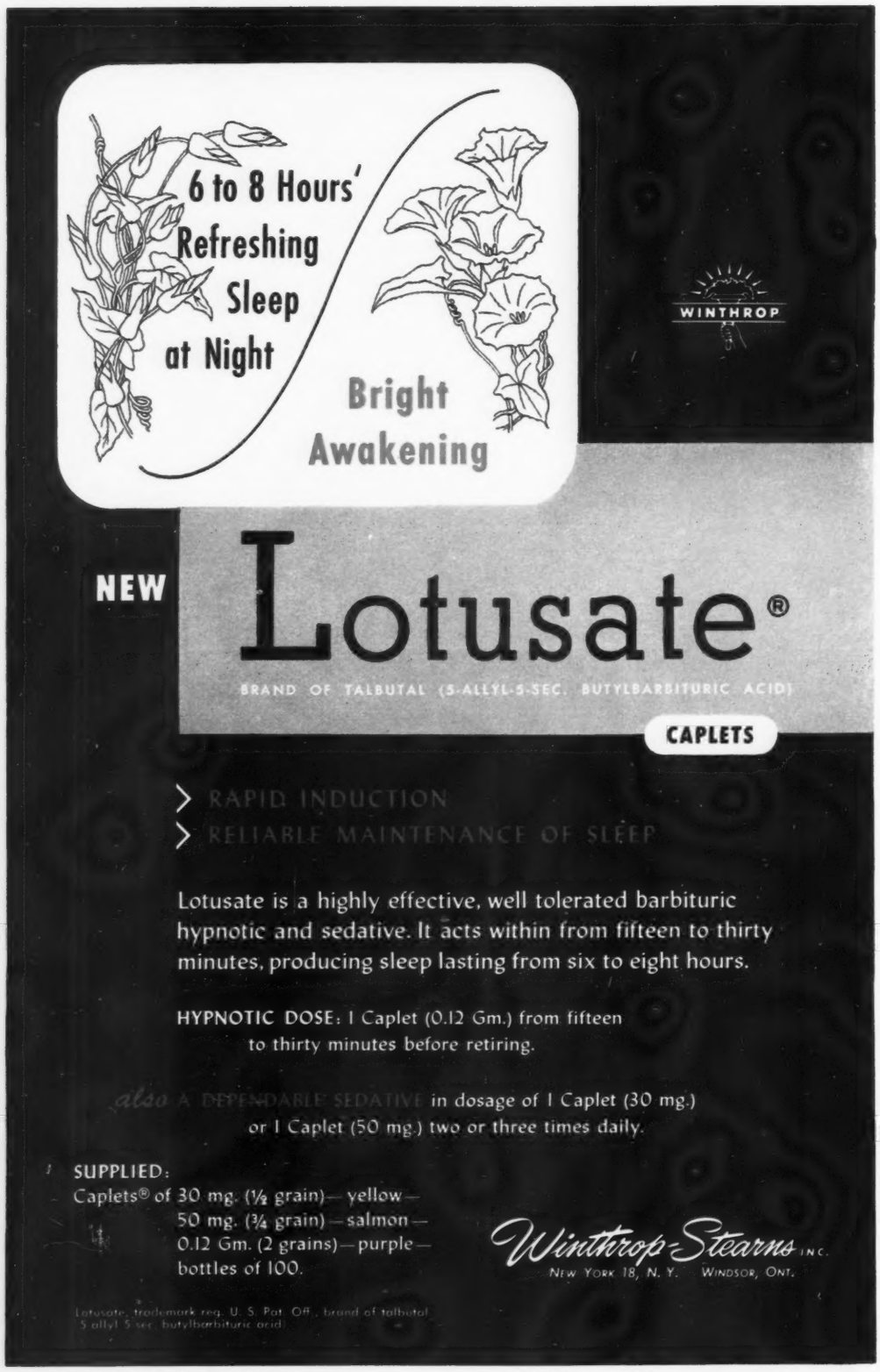
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FIRST THOUGHT IN HYPERTENSION

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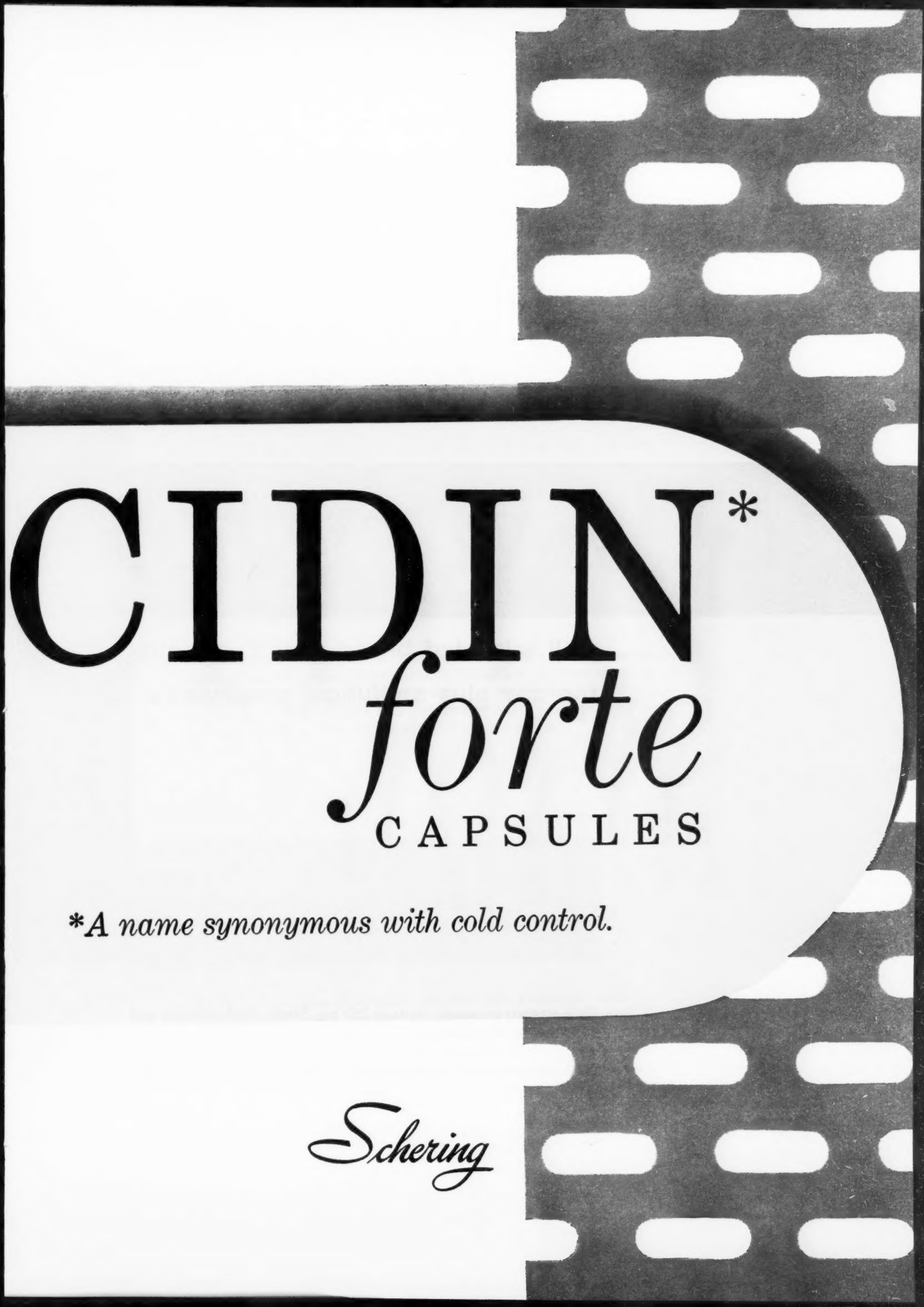
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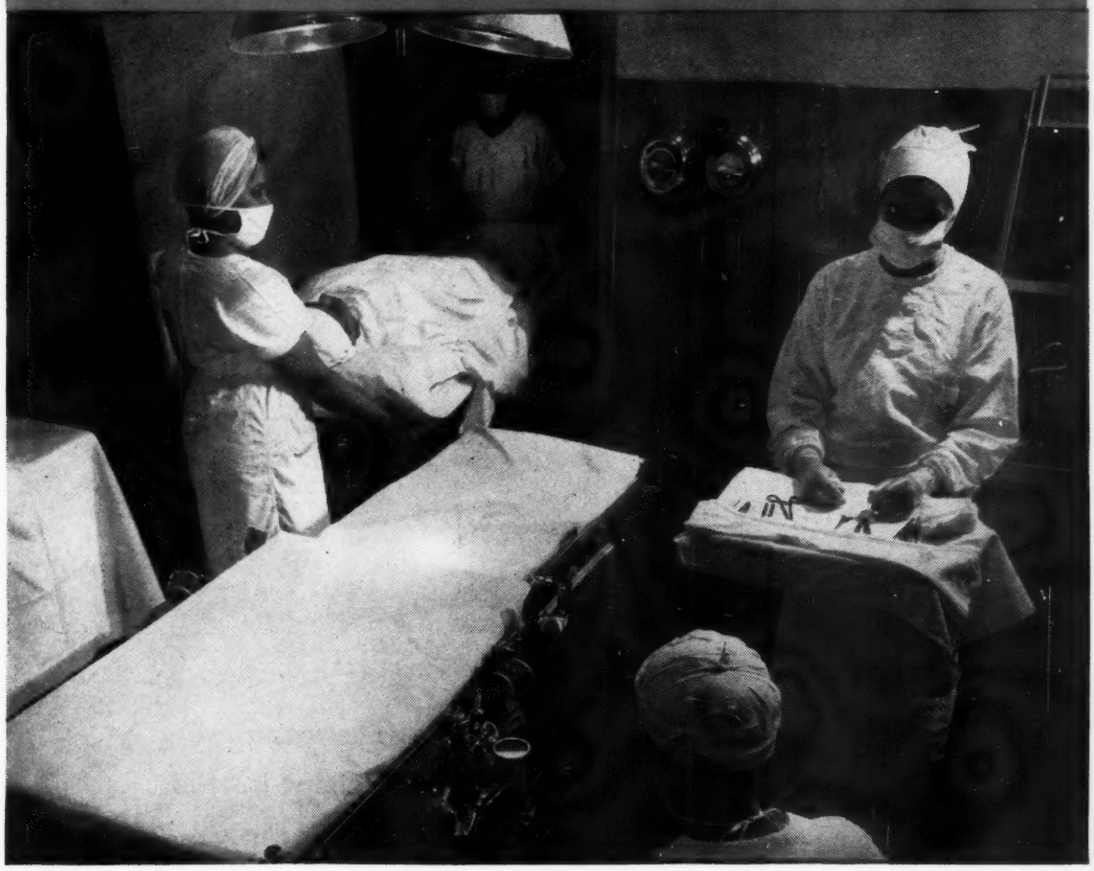

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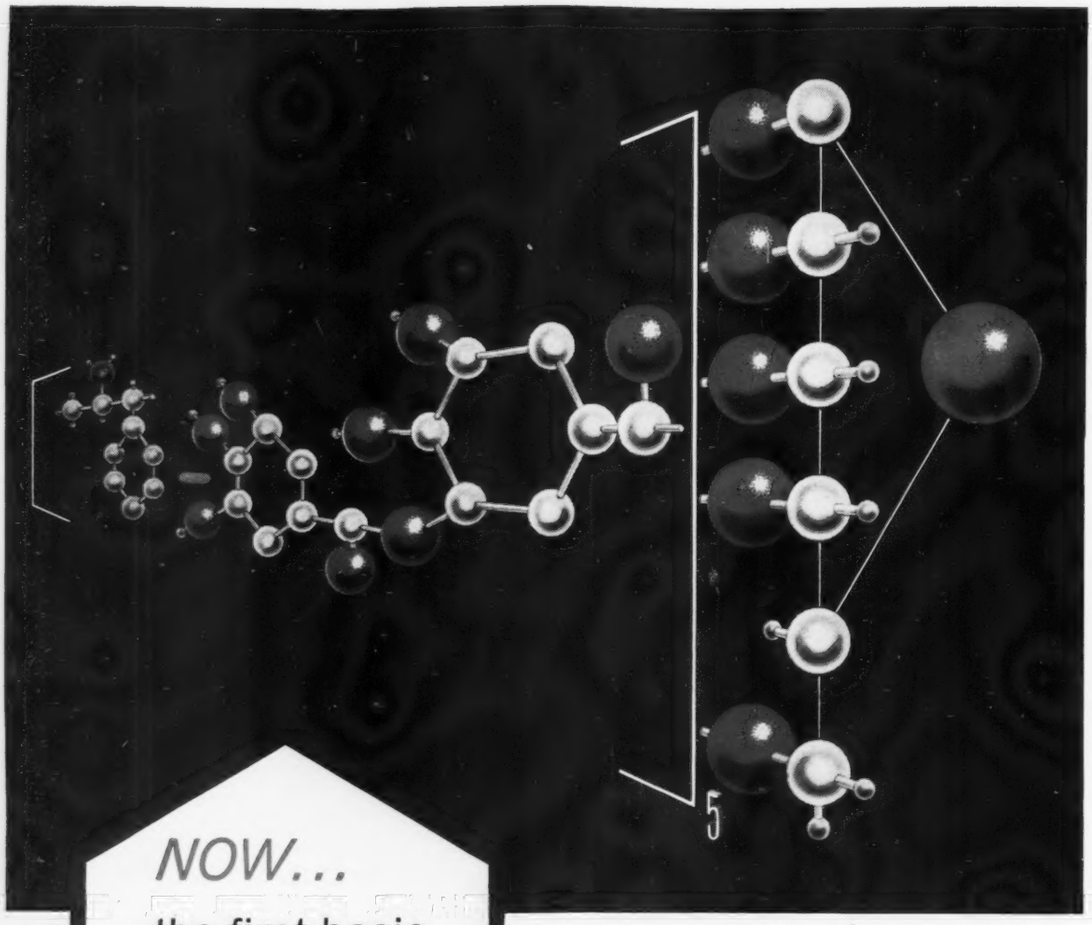

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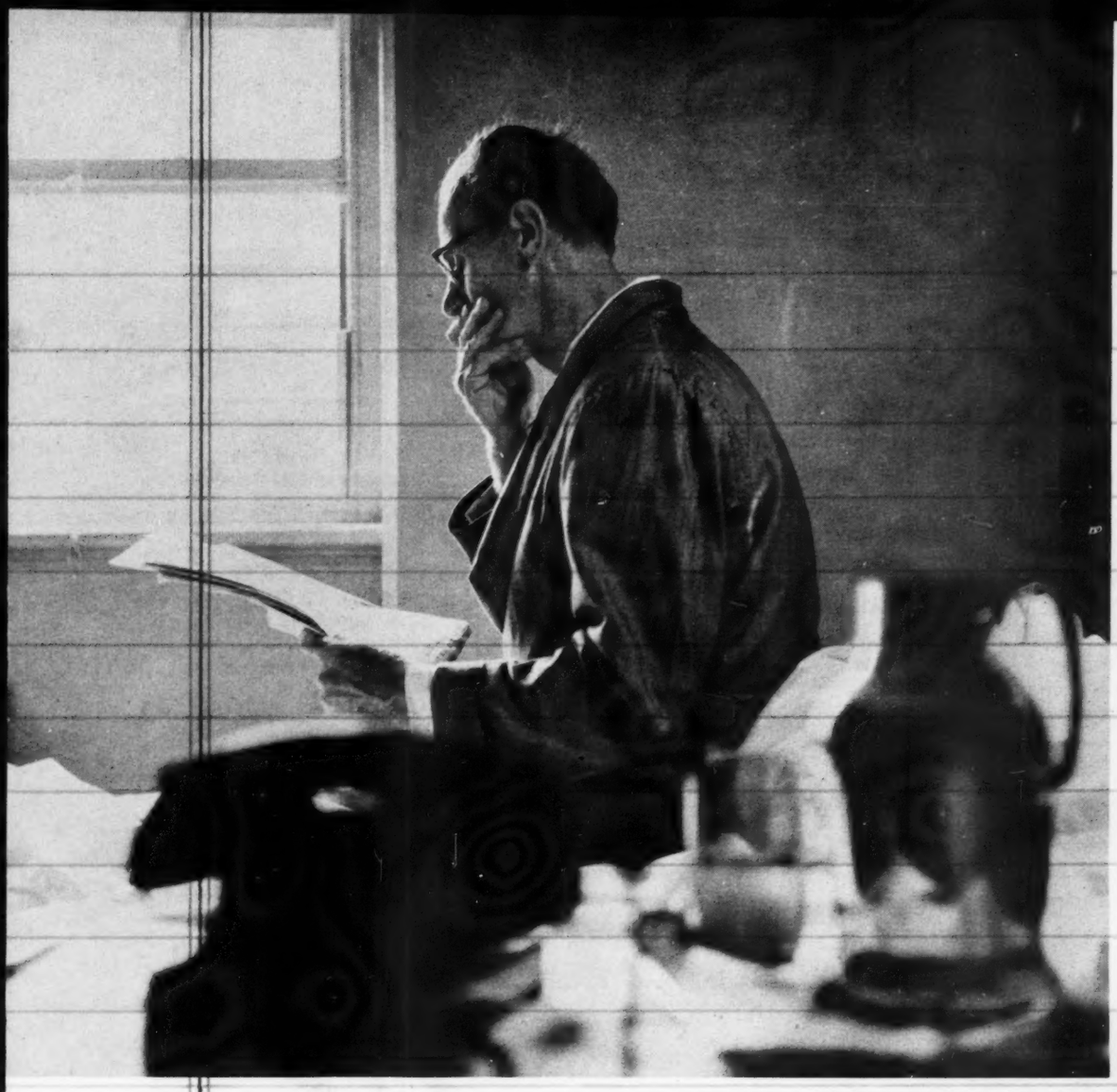

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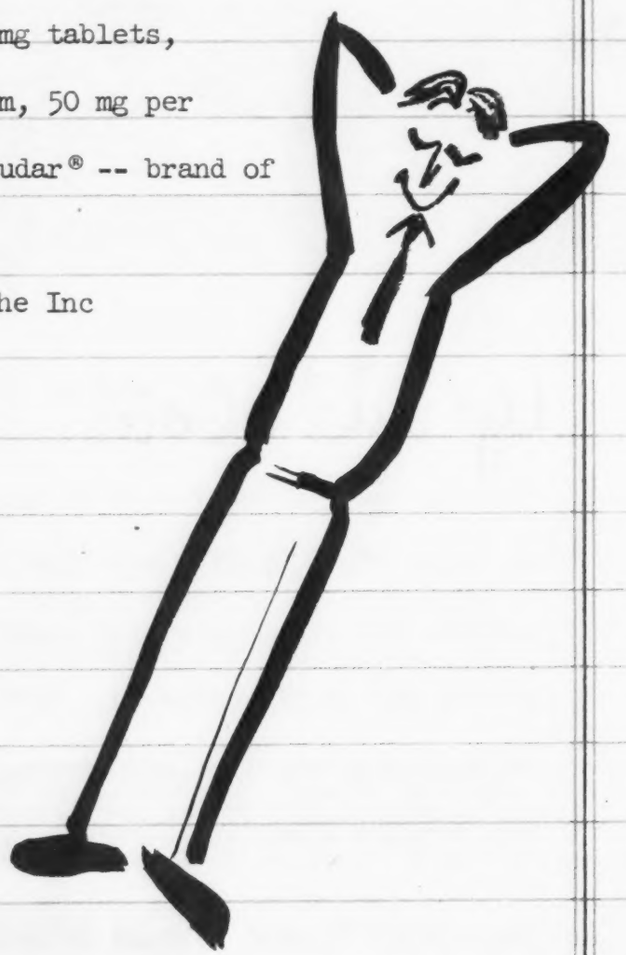

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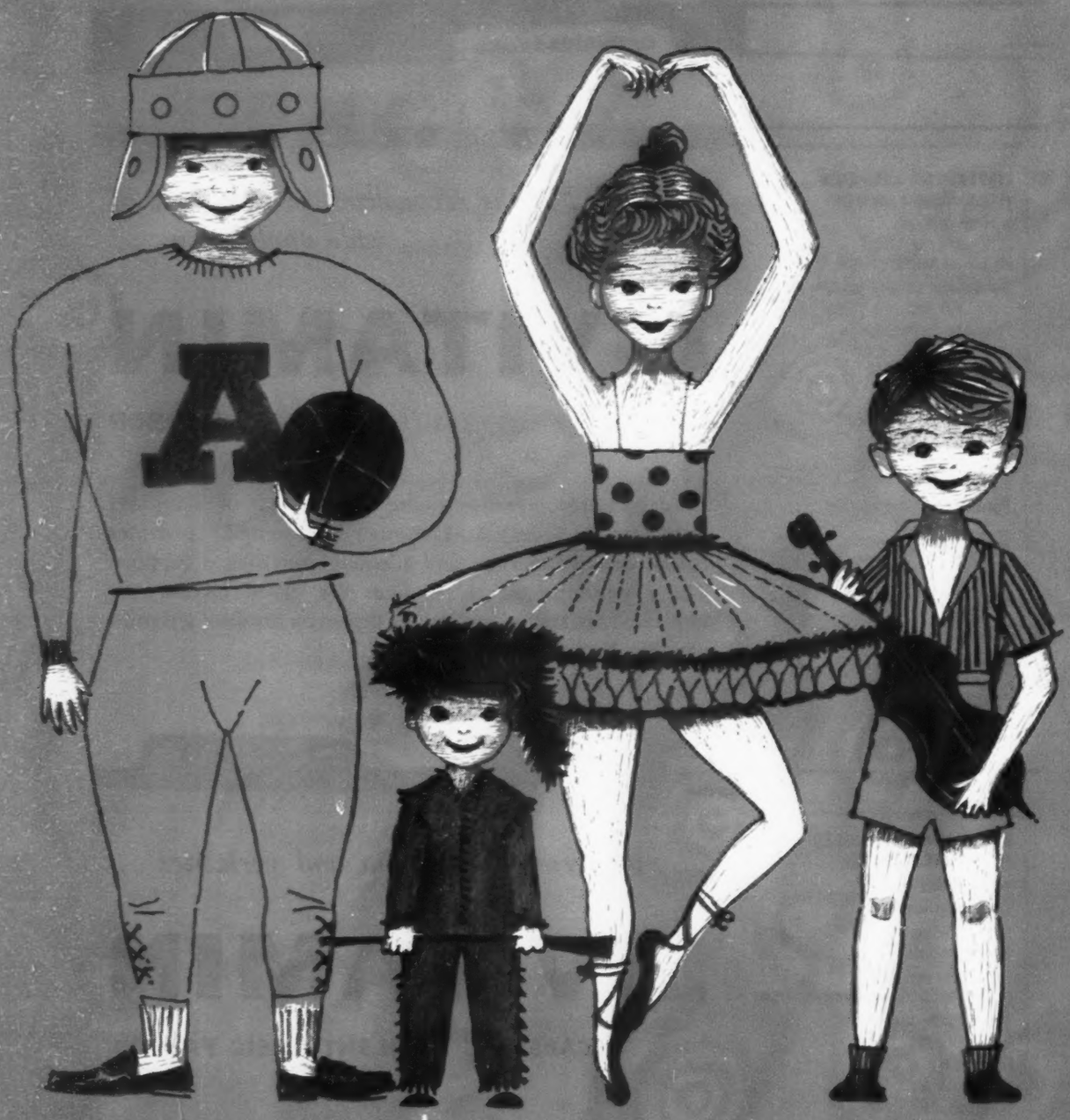

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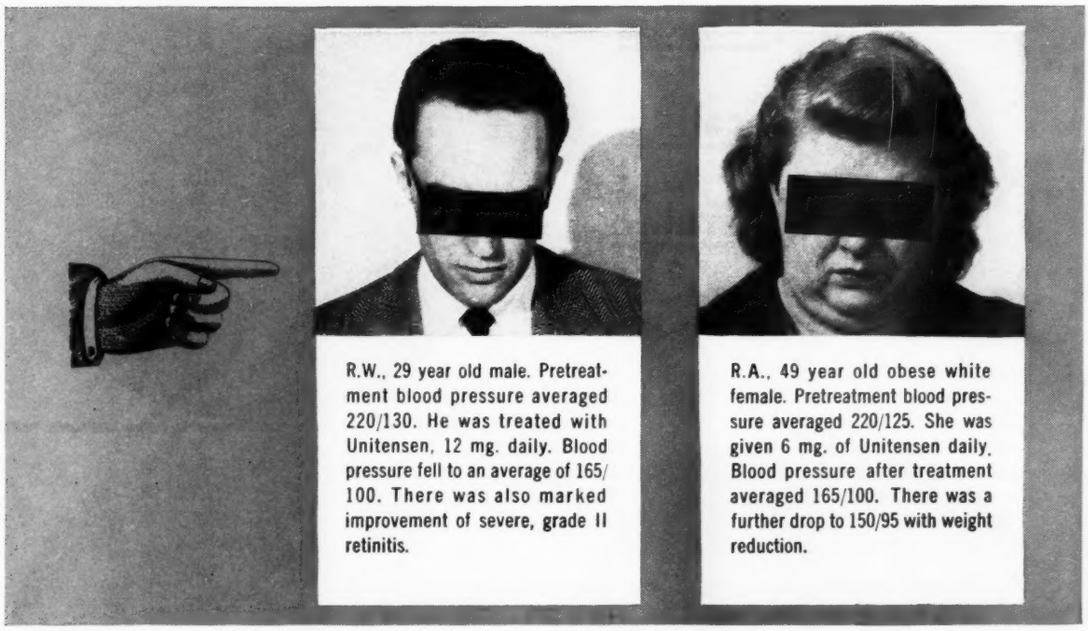

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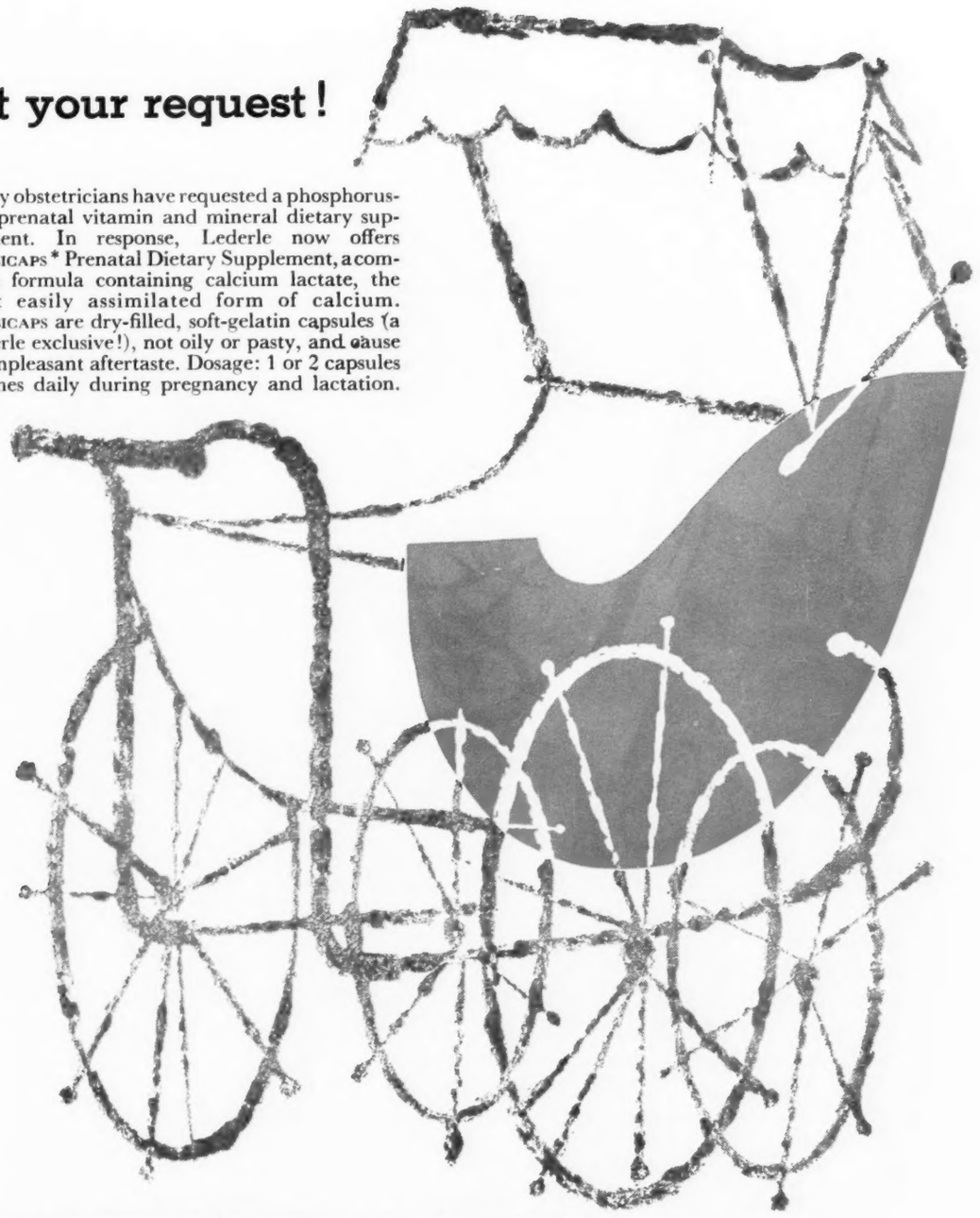

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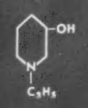

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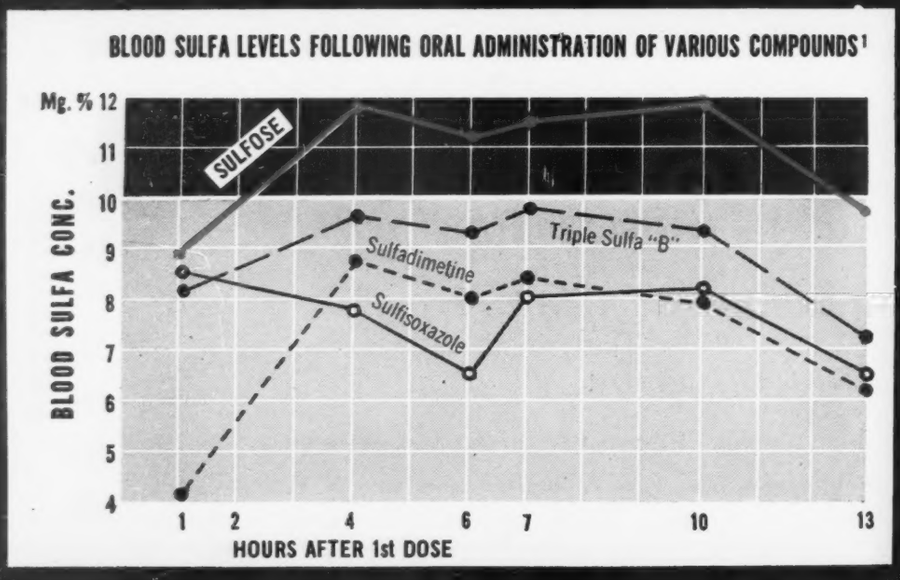

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1. Berkowitz, D.: Antibiot. & Chemo. 3:618 (June) 1953

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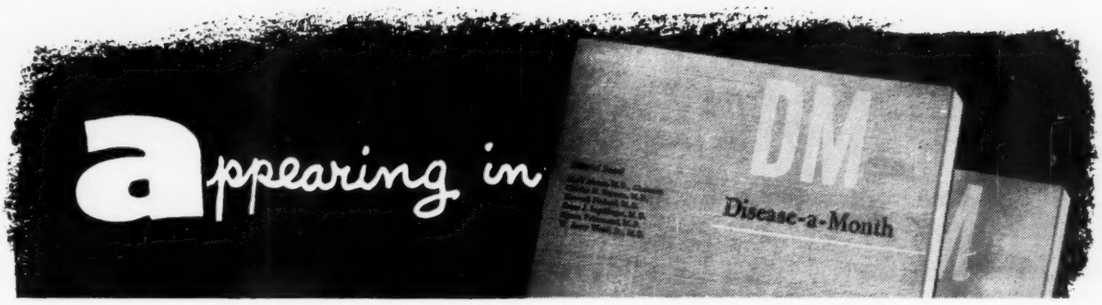

October issue of

DM

Disease-a-Month Series

Chronic and Recurrent Diarrhea

BY THOMAS P. ALMY, M.D.

Associate Professor of Medicine, Cornell University

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Dr. Almy's monograph on Chronic and Recurrent Diarrhea in the October issue is typical of what you get in DM, and how. Below is a list of some of the future DM's and the authorities writing them.

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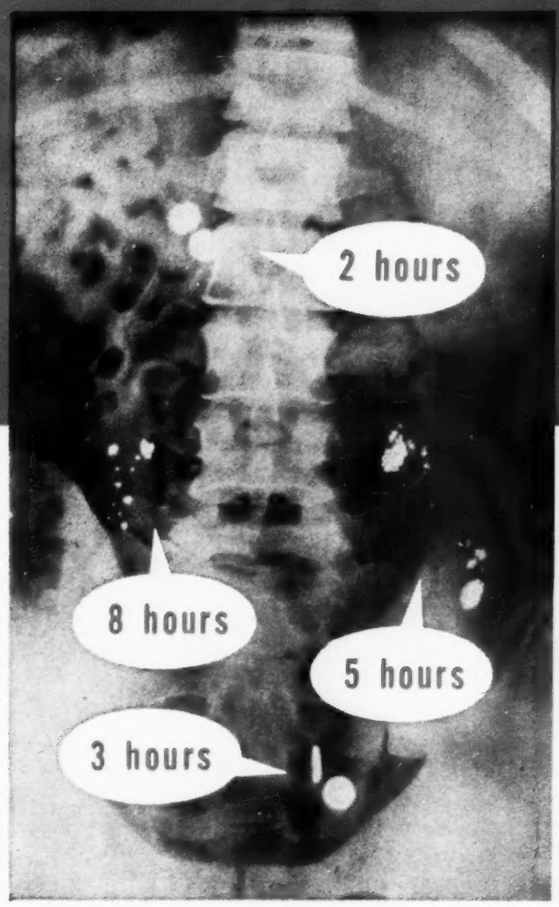

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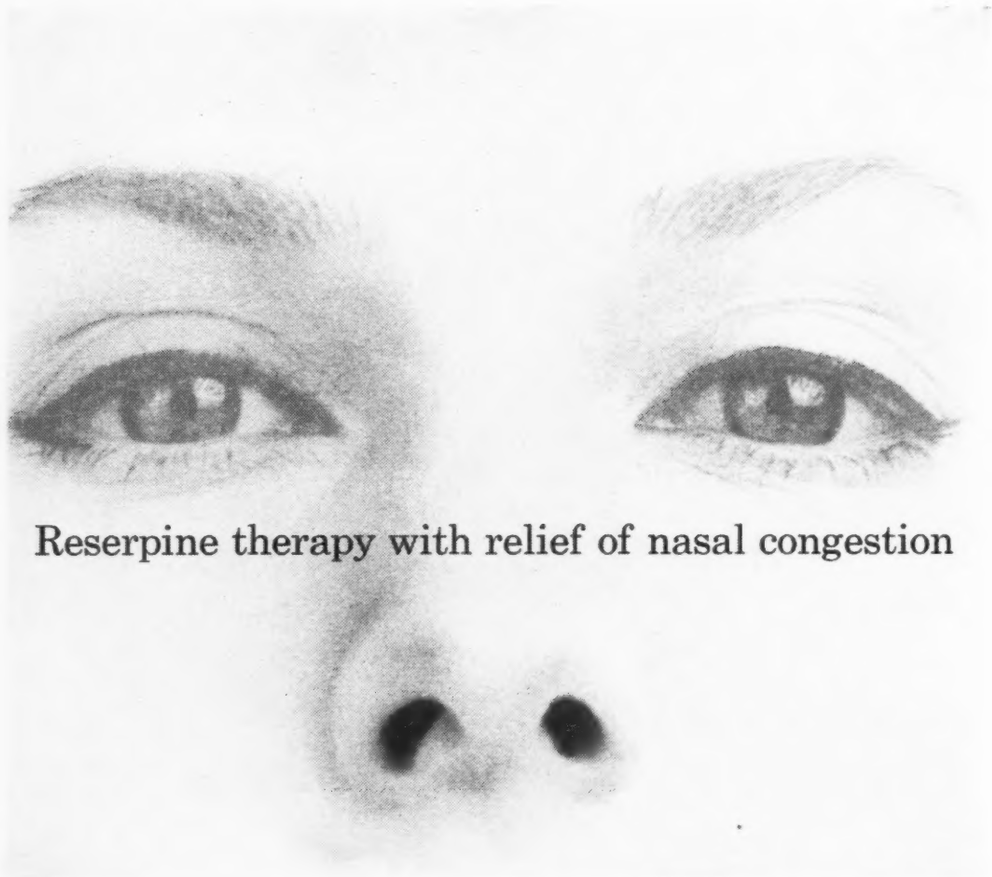

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The American Journal of Medicine

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Editorial

The Interrelationships of Ventilation, Circulation and Metabolism

COMPARED to the vast amount of investigation of circulatory mechanics little attention has been given to the ventilatory counterpart of the homeostatic mechanism. Much recent work has been done in the laboratory of the physiologist to remedy this defect but so far little of it has permeated clinical thought.

The superficial aspects of the ventilatory act have long been familiar to clinicians; such aspects include the types of breathing described by Kussmaul, Cheyne-Stokes and Biot, the orthopnea of heart failure or asthma and the rapid shallow breathing of pneumonia. Interspersed in the clinical jargon of the day frequent surmises can be heard that this or that anxious or hysterical person exhibits a "hyperventilation syndrome," yet rarely is an effort made to verify the conjecture even by testing Chvostek's sign. This is understandable as regards laboratory confirmation because of the ephemeral nature of the phenomena and the elaborate equipment requisite for the proof. Hypoventilatory syndromes with respiratory acidosis are recognizable in morphine poisoning, emphysema with bronchitis or bronchitic asthma or in some cases of poliomyelitis, and the clinical surmise can be checked by determinations of the pH and tensions of the respiratory gases in the arterial blood. It was not easy to recognize that in many patients with poliomyelitis hyperventilation occurred in the respirators and this was often the cause of the subsequent difficulty in weaning them from the "iron lung." This is apparently due to the increased sensitivity which the respiratory center acquires as a part of its adaptation to low carbon dioxide tensions resulting from prolonged hyperventilation.

It is with the aberrations of homeostasis that the clinician is primarily concerned. To maintain constancy of the internal environment of the body, in view of the wide variations in the metabolic demands of the cells, requires the closest coordination of the ventilatory events with those taking place in the circulation. Disturbance of the normal relationships between ventilation and blood flow is immediately reflected in the tensions of the alveolar gases and their equilibration with those of the blood. Unless these changes are promptly compensated for by electrolyte shifts between plasma and cells, the degree of alkalinity of the blood may be altered until a slower form of compensation is effected, primarily by the activity of the kidneys and also by the gastroenteric mechanisms for altering the base, chloride and phosphate of the blood. Conversely, when the primary disturbance occurs in these latter mechanisms or through some alteration in the intermediary metabolism, the most prompt reactions toward homeostasis are those affected by altering ventilation and blood flow, assuming, of course, that the coordinating activity of the nervous system is not impaired by narcosis, blocking agents or other pharmacodynamic effects which may alter the sensitivity of the nervous system mechanism.

In recent years an enormous amount of work has gone into the systematic mapping out of the afferent nervous system pathways from various

types of receptors distributed widely over the body, by means of which the modifications of ventilation and circulation are mediated. These receptors are of two general types, those which are stimulated mechanically and are known as "stretch receptors," and those which are stimulated chemically by changes in reaction or changes in CO_2 and O_2 tension and are known as "chemo-receptors." The progress of this work has been well reviewed recently by Dawes and Comroe.[1]

The mechanics of respiration was the subject of a review by W. O. Fenn in this journal in 1951.[2] A valuable compilation of the many papers from Fenn's laboratories was published in a technical report of the United States Air Force in the same year.[3] Rahn[4] in one of these papers (and Riley and Cournand[5] independently) deals very clearly with the relationship of ventilation to blood flow in the pulmonary gas exchange of normal subjects. While this implies normal regulatory mechanisms and no abnormal barriers to diffusion of gases between the alveoli and the pulmonary capillaries, such as may exist under pathologic conditions, these papers will remain important guides to clinical thinking when dealing with such conditions. Rahn has derived an equation from the blood flow equation of Fick and the alveolar ventilation equation of Fenn. With the aid of the Henderson diagram for blood and the Fenn diagram for gas respiratory quotient, Rahn was able to represent graphically all the simultaneous tensions of oxygen and carbon dioxide which satisfy the combined equation in which the use of alveolar ventilation V_a and blood flow F as a ratio, V_a/F, makes it unnecessary to take account of the level of metabolism. Each point on the curve represents a particular V_a/F ratio with its corresponding respiratory quotient. At the usual or average respiratory quotient of 0.8 the V_a/F ratio is 1.0 and the corresponding partial pressures of O_2 and CO_2 are 100 and 40 mm. Hg respectively. The mean of the normal range of alveolar respiratory quotients is from 0.7 to 1.0; with mean values above 1.0 the V_a/F ratios are increased and relative hyperventilation is indicated, while respiratory quotients below 0.7 and correspondingly low V_a/F ratios indicate relative hypoventilation.

In clinical thinking the concept of this ratio becomes important in that hyperventilation may be dependent as much upon failure of the blood flow to maintain parity with the ventilation as upon augmentation of the ventilation *per se*. Conversely, hypoventilation may depend as much upon an increased blood flow with which the ventilation does not maintain parity as upon depression of the ventilation.

In a recent paper by Alexander, Spalter and West[6] the hyperventilation of salicylate toxicity has been shown to be due to increased respiratory sensitivity to the carbon dioxide stimulus. In this issue of the Journal, Tenney and Miller[7] have studied the circulatory, ventilatory and metabolic effects of this drug. They, too, have found that salicylate exerts a direct respiratory stimulant action on the medulla, independent of aortic or carotid chemoreceptors. They have added that salicylate is a profound metabolic stimulant acting primarily on skeletal muscle. The circulatory response to salicylate is affected partially by an increase in cardiac output and to a large extent by a widening of the A-V oxygen difference. The net result was a lowering of the $P_A\ CO_2$ and a rise in pH. In other words, the V_a/F ratio was increased by the failure of the cardiac output to increase in proportion to the rise in ventilation and metabolism.

In a previous paper[8] Tenney pointed out that the diminished response of the respiratory center of a patient with emphysema is proportional to the degree of CO_2 retention. In general, he finds that the sensitivity of the respiratory center, as indicated by the slope of a stimulus response curve, appears to change in a manner inversely proportional to the degree of CO_2 retention.

[1] Dawes, G. S. and Comroe, J. H., Jr. Chemo-reflexes from the heart and lungs. *Physiol. Rev.*, 34: 167, 1954.

[2] Fenn, W. O. The mechanics of respiration. *Am. J. Med.*, 10: 77, 1951.

[3] Fenn, W. O., Otis, A. B. and Rahn, H. Studies in respiratory physiology, chemistry, and mechanics of pulmonary ventilation. Air Force Technical Bulletin. No. 6528, August, 1951. Published by U. S. Air Force, Wright-Patterson Air Force Base, Dayton, Ohio.

[4] Rahn, H. A concept of mean alveolar air and the ventilation-blood flow relationships during pulmonary gas exchange. *Am. J. Physiol.*, 158: 21, 1949.

[5] Riley, R. L. and Cournand, A. "Ideal" alveolar air and analysis of ventilation-perfusion relationships in the lungs. *J. Applied Physiol.*, 1: 825, 1948–49.

[6] Alexander, J. K., Spalter, H. F. and West, J. R. Modification of the respiratory response to carbon dioxide by salicylate. *J. Clin. Investigation*, 34: 533, 1955.

[7] Tenney, S. M. and Miller, R. M. The respiratory and circulatory actions of salicylate. *Am. J. Med.*, 19: 498, 1955.

[8] Tenney, S. M. Ventilatory response to carbon dioxide in pulmonary emphysema. *J. Applied Physiol.*, 6: 477, 1954.

In Tenney's studies on salicylate an interesting and important difference was found when oral administration is compared with intravenous injection of the drug. With oral administration the respiration is stimulated but the increase in the sensitivity of the center does not occur until the kidneys have had time to excrete base and lower the bicarbonate level of the plasma. Thus the person who receives salicylate by mouth reacts as does the person who is adapting himself to the hypoxia of high altitude. When, on the other hand, salicylate is given intravenously the respiration is stimulated to the production of an alkalosis, yet the center is not rendered more sensitive because there is no immediate compensatory lowering of the bicarbonate level, and the metabolic effect of the drug has greatly increased CO_2 production.

These experiments of Tenney illustrate beautifully the precise correlation that must exist between ventilation, blood flow and metabolism if homeostasis is to be maintained.

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Clinical Studies

The Respiratory and Circulatory Actions of Salicylate*

S. M. Tenney *and* R. M. Miller

The voluminous literature on the salicylates attests not only to their importance but also to the uncertainties and controversies associated with their action. Comprehensive reviews[1–3] over the years have emphasized many of the areas of doubt. Most authors agree that respiratory stimulation is an important action of the salicylates but precise quantitation of this response is wanting. The locus of action is not certain, although there are reports in the literature which purport to show that peripheral receptor systems are essential if stimulation is to occur.[4–7] Direct medullary stimulation has been implied in many instances but remains unproven. The important question of salicylate effect on the acid-base balance of the body still remains controversial, although there is accumulating evidence which indicates that respiratory alkalosis is the most common result in adult man.[8] Arguments persist as to whether there is a transient period of acidosis which serves as the initial respiratory stimulant. The effect of salicylate on gaseous metabolism[9,10] has been largely neglected and may serve as a major clue to the final effects on both the respiratory response and the ultimate acid-base pattern. Finally, the response of the circulatory system, which must serve as the integrator between lung and tissue in the altered respiratory state of salicylism, has not been adequately studied.

Experiments (designed for both man and dog) were performed to answer some of these problems and they form the subject matter of this report.

METHODS

Mongrel dogs anesthetized with intravenous sodium pentobarbital (27 mg./kg. body weight) constituted the principal experimental preparation. Attention was directed to maintaining as nearly as practicable a steady state under anesthesia. This was done by continuing an intravenous drip of low concentration pentobarbital in saline solution (half of the calculated anesthetic dose in 500 cc. saline solution) at the rate of approximately 40 drops per minute. An endotracheal tube was inserted and fitted to a low resistance check valve. Alveolar (end tidal) samples were collected by syringe from an endotracheal polyethylene catheter. One ml. aliquots were aspirated at end tidal flow for five successive breaths and analyzed for CO_2 and O_2 by means of the Scholander-Roughton micro-gas analyzer.[11] Arterial blood was collected from the carotid artery and mixed venous blood from the right ventricle via catheter. Blood samples were analyzed for CO_2 and O_2 contents by the method of Van Slyke and Neill.[12] Whole blood pH was determined immediately at 38°C. by the Beckmann model G pH-meter. Intravascular pressures were recorded with Statham strain gauges and a Sanborn polyviso oscillograph.

All observations on man were made while the subject lay comfortably in the supine position. Oxygen consumption was determined under basal conditions. Ventilation measurements were made through a mouthpiece and check-valve arrangement, the input of which led from a Douglas bag containing the desired inspiratory gas mixture and the outlet connected to a low resistance gas meter previously calibrated at both high and low flow velocities against a spirometer. Respiratory frequency was recorded with pneumograph. The inspired gas mixtures employed were 100 per cent O_2, 3 per cent CO_2 in 97 per cent O_2, and 5 per cent CO_2 in 95 per cent O_2. These mixtures were breathed for

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fifteen minutes each but the mean minute volume and respiratory frequency for only the last five minutes were computed. All volumes were corrected to body temperature and pressure, saturated with water vapor (BTPS). At the end of each run a Haldane-Priestley alveolar air sample was collected and analyzed for CO_2 and O_2. The respiratory dead space was measured in each subject by determining the alveolar and expired CO_2 concentrations and applying the Bohr equation. Alveolar ventilation was then calculated in the usual way [alveolar ventilation = minute volume expired − (respiratory frequency × dead space volume)]. The normal subjects were all trained in respiratory maneuvers, and at least three consistent control runs were required before evaluating effects of the drug. Acute experiments involving intravenous salicylate were preceded by a control run on all gas mixtures immediately prior to exhibition of a drug. The salicylate response was observed by initiating measurements twenty minutes after drug administration.

Sodium salicylate solution was always employed in a concentration of 1 gm. per 5 cc., pH 3.5.

Patients on salicylate therapy were studied in the same manner except that no data were obtained on CO_2 breathing.

RESULTS

Acute Response to Sodium Salicylate in the Dog. Figure 1 illustrates a representative experiment in which the immediate changes following the intravenous injection of sodium salicylate (100 mg./kg. body weight) are recorded. Following an approximately one-minute latent period, ventilation was enhanced and the alveolar CO_2 tension began to fall. The only detectable change in arterial pH was a continuing rise from the normal value concomitant with the fall in CO_2 tension. No early fall in pH preceding respiratory stimulation was ever observed. Beginning shortly after the initial increase in ventilation there developed a gradual increase in oxygen consumption which reached its maximum in about twenty-five minutes. At this dosage range the oxygen consumption was nearly doubled. The early hyperventilation was attended by an increase in the respiratory exchange ratio but by the time oxygen consumption had reached its maximum the respiratory quotient had returned to control values, and the oxygen consumption and carbon dioxide production were equivalent. That the increase in oxygen consumption is not secondary to the increase in ventilation will be shown subsequently. Indeed, the major part of the increase in ventilation after the first five minutes of the effect of the drug is secondary to the augmented CO_2

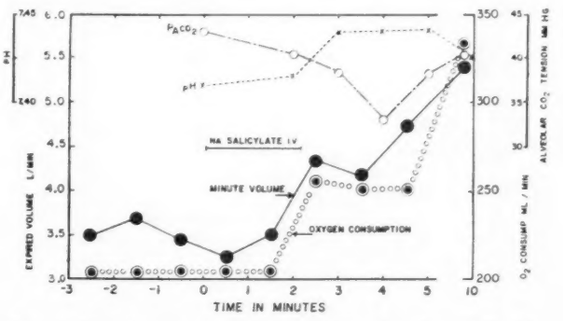

FIG. 1. Respiratory responses of the dog immediately following the intravenous injection of 100 mg./kg. body weight sodium salicylate.

production. It is for this reason that the later increase in ventilation is not attended by much further fall in alveolar CO_2 tension or further rise in arterial pH. In some instances this metabolic demand on ventilation may exceed its response, particularly under deep anesthesia, and a rise in CO_2 tension in the blood and alveolar air may result. Some of the questions which such observations pose are considered in the following experiments.

Metabolic Effect of Salicylate. The pronounced effect of salicylate on respiratory gas metabolism is unequivocal. Figure 2 illustrates the dosage-response relationship of this effect. Apparently there is a maximum change in oxygen consumption achieved at about 100 mg./kg. for sodium salicylate. At higher levels the range of response is wide; at very high doses (150 mg./kg.) many individuals may respond less than with a smaller dose.

The source of such a major metabolic effect is probably in skeletal muscle. The predicted response to a dose of 100 mg./kg. is achieved in both the eviscerated dog and the "functionally hepatectomized" dog (Eck's fistula with hepatic artery ligation), indicating that the liver is not the principal source of increased oxidative requirement. Figure 3 illustrates that the response is independent of central and peripheral nervous control. Three decapitated dogs revealed the predicted metabolic response to salicylate; a similar number under the influence of curare showed no difference in this response

from intact dogs. The metabolic response is also readily exhibited in the presence of established adrenal blockade (dibenzyline®) so that the "calorigenic action" of epinephrine is not implicated. This would appear to establish that the response reflects metabolic processes in the

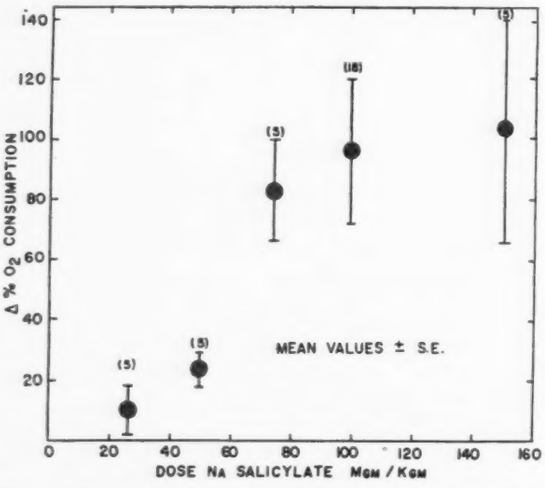

FIG. 2. Dose-response data for sodium salicylate effect on oxygen consumption in the dog; determinations made twenty-five minutes after drug administration. Numbers in parentheses refer to number of experiments performed to define each mean point.

peripheral tissues. Recent *in vitro* studies support this contention,[13] although Lutwak-Mann could detect no significant change in the oxygen consumption of liver slices except in the presence of high concentrations of salicylate when it acted as a metabolic depressant.[14]

The respiratory response to salicylate in the intact dog is a summation of (1) direct central stimulant action and (2) increased metabolic production of carbon dioxide. The magnitude of the latter stimulus may be seen in isolation if ventilation is held constant throughout the experiment. Figure 4 illustrates a typical experiment in which salicylate was administered to a dog already under the influence of curare, and in which ventilation was artificially maintained at a constant rate in a whole body respirator. As the metabolic effect develops the blood reaction becomes acid and the tension of carbon dioxide rises in the alveolar air. The extent of this acute respiratory acidosis is directly proportional to the increase in metabolic CO_2 production. It is clear from these experiments that the increase in oxygen consumption observed in the intact dog is not secondary to hyperventilation.

Salicylates as Direct Central Nervous Stimulants. The observed fall in alveolar CO_2 tension and

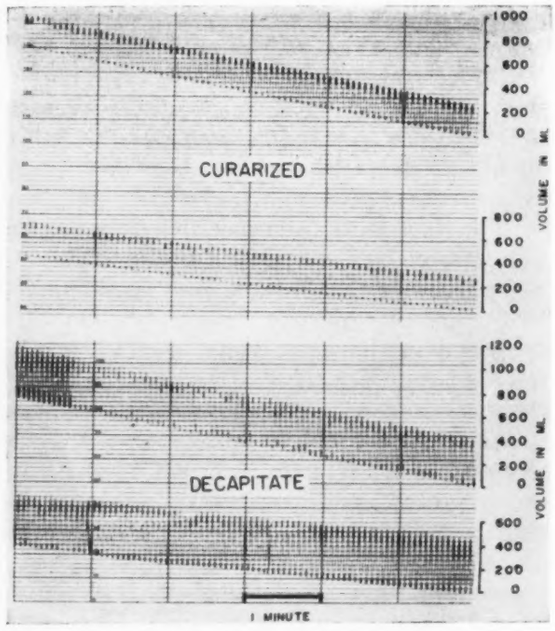

FIG. 3. Segments of spirometer tracings of decapitated and curarized dogs maintained at constant ventilation in whole body respirator. In each pair the lower trace is control and the upper is the record made twenty-five minutes after salicylate (100 mg./kg.).

rise in arterial pH in the intact dog following salicylate administration implies a direct action on the ventilatory mechanism. Experiments have been interpreted as proving that this effect is mediated via peripheral receptors since it could not be demonstrated in the vagotomized animal.[4,5,6,7] It should be emphasized, however, that in each instance two large salicylate doses were administered within a short time interval, once before and once following vagotomy. Lack of ventilatory response to the second dose cannot be accepted as final evidence for the necessity of vagal pathways since the same lack of response is seen in the intact dog when a second dose closely follows the first.

If the major part of the ventilatory increase is secondary to the metabolic stimulating action of salicylate, it would be anticipated that the medullary centers only would be involved since this is the locus of action for CO_2. The direct drug stimulating effect might, however, depend upon a different area. That this area is not the chemoreceptor of the carotid or aortic arteries is shown by experiments of the type illustrated in Figure 5. Both vagi were severed and both carotid bodies denervated in the dog. Functional denervation was established since no respiratory stimulation occurred when the

animals breathed 5 per cent O_2 in 95 per cent N_2. However, immediately after administration of sodium salicylate intravenously there was an increase in the minute volume expired. The subsequent sequence of events in the vagotomized animal differed from the intact preparation

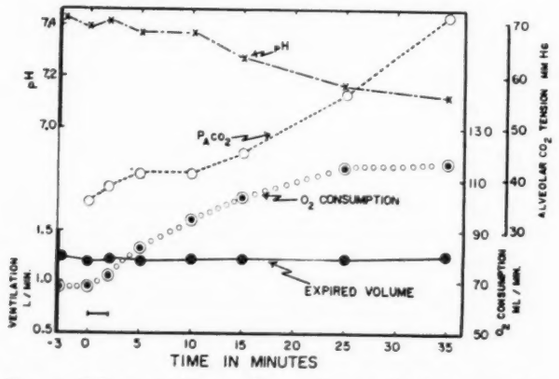

FIG. 4. Effect of 100 mg./kg. sodium salicylate on acid-base balance and respiratory gas metabolism of curarized dog in whole body respirator maintained at constant ventilation; drug administered at zero time over two minute time interval.

only in that there was less increase in respiratory frequency.

That the locus of action of direct salicylate respiratory stimulation is in the central nervous system may be shown by applying low concentrations of salicylate to the region of the medulla.

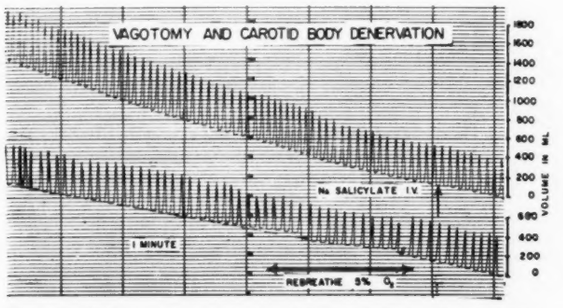

FIG. 5. Spirometer record of dog with both vagi sectioned and both carotid bodies denervated; ventilation is not altered by 5 per cent O_2 in 95 per cent N_2 but increases after intravenous injection of sodium salicylate (100 mg./kg.).

Three dogs studied in this manner gave consistent results, and a representative experiment is noted in the graphs in Figure 6. A needle was placed in the cisterna magna with the dog maintained in a slightly head-down position. Control observations were afforded by slowly withdrawing 2 ml. of cerebrospinal fluid and replacing an equal volume of phosphate buffer at pH = 7.34. Minimal changes in ventilation occurred. Again 2 ml. were withdrawn, and a solution of sodium salicylate (1:500) in phosphate buffer adjusted to pH = 7.34 was injected. This was followed by a prompt and dramatic increase in ventilation, a fall in alveolar CO_2 tension and a rise in arterial pH, which oc-

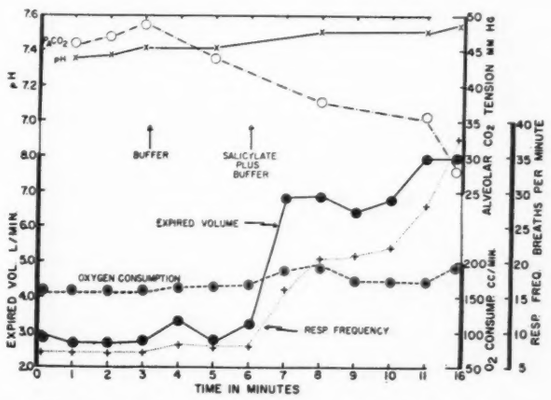

FIG. 6. Respiratory changes following injection of 2 cc. 1:500 sodium salicylate in buffer into cisterna magna of dog; see text.

curred without any attendant rise in oxygen consumption. These effects then represent only the direct stimulating action of salicylate on the central nervous system. It is of considerable interest that as this action became more marked the respiratory frequency increased to such a degree that dead space ventilation occupied a larger fraction of the minute volume and effective alveolar ventilation remained essentially constant in spite of the continuing increase in minute volume expired. It is for this reason that the alveolar CO_2 tension and arterial pH levelled off after the first few minutes, but at a new level characteristic of respiratory alkalosis.

TABLE I
PHYSICAL DATA OF NORMAL SUBJECTS

Subject	Age, Sex	Height (cm.)	Weight (kg.)	Surface Area (M^2)	Dead Space Volume (cc.)
R. M.	34, M	183	77	2.0	118
A. M.	26, F	174	59	1.72	114
B. S.	27, M	186.5	95	2.2	100
M. C.	28, F	171	60	1.7	111
M. T.	32, M	176	68	1.85	160

Salicylate Action in Normal Man. Five normal adult subjects with physical characteristics cited in Table I were studied in the manner described

under the section on methods. Table II lists the respiratory data obtained following intravenous injection of 2 gm. of sodium salicylate. Immediate respiratory stimulation was observed in each instance with development of a slight respiratory alkalosis. A group mean increase in oxygen consumption of 18 per cent was noted. Our interpretation of these effects is the same as for similar experiments previously cited for the dog. Also listed in Table II are the respiratory data obtained in these same five subjects as they ingested 8 gm. of acetylsalicylic acid (enteric-coated) per day for a period of three days. Continued hyperventilation is in evidence.

TABLE II

RESPIRATORY DATA IN NORMAL MAN

Period	Subject	Plasma Salicylate (mg. %)	Oxygen Consumption (ml./min.)	Expired Volume, L./min. (BTPS)			Alveolar CO_2 Tension, mm. Hg			Respiratory Frequency, Breaths/min.		
				Room Air	3% CO_2	5% CO_2	Room Air	3% CO_2	5% CO_2	Room Air	3% CO_2	5% CO_2
Control	RM (5)*	0	275	7.59	16.25	27.7	41	43.2	47	7.9	13.5	16
	AM (3)	0	221	4.28	9.7	12.41	41.3	43.7	48.7	5	8.2	9.7
	BS (4)	0	273	8.1	16.13	27.9	39	41.7	44.3	8.1	10	13.4
	MC (3)	0	208	4.97	7.63	10.58	44.4	46.3	51.8	8	9.4	10.4
	MT (3)	0	224	6.7	13.4	19.3	38.7	42.3	44.7	8.3	11.2	13.4
	Mean	..	239	6.33	12.62	19.57	40.9	43.4	47.3	7.5	10.5	12.6
Twenty-five minutes after 2 gm. Na salicylate intravenously	RM (2)	22	275	8.62	19.25	32.2	39	42	49	9.0	17.2	18
	AM (2)	22	277	5.56	11.11	14.75	37.6	....	45.4	5.2	6.4	7.8
	BS (2)	22	296	7.68	19.6	34.6	37.3	37.3	40.7	7.6	12.8	17.8
	MC 2)	27	233	5.95	7.65	11.32	44.5	48.6	52.0	7.8	9.2	10.8
	MT (2)	27	239	8.55	13.05	23.0	35.0	36.5	43.2	8.6	12.6	16.4
	Mean	24	264	7.27	14.14	23.2	38.7	41.1	46.0	7.6	11.6	14.2
Oral aspirin, 2nd day, 3 gm./day	RM	21	...	7.9	18.2	24.1	38.4	43.7	44	11.4	15.2	19
	AM	32	...	5.71	12.85	17.6	36.4	41.4	46.2	5.0	7.6	8.6
	BS	29	...	9.1	27.2	36.6	37.6	37.3	40.4	9.6	21.7	22.6
	MC	35	...	6.94	10.7	11.82	39.5	43.2	49.2	8.6	11.6	14
	MT	37	...	7.68	15	27.3	37.8	36.2	43.6	9.6	13	17.4
	Mean	31	...	7.47	16.79	23.5	37.9	40.3	44.7	8.8	13.8	16.3
24 hrs. after oral drug discontinued	RM	23	...	10	22.8	33.7	38.4	42.5	42.5	14.4	13.9	16
	AM	23	...	5.44	11.2	15.65	37	41.2	42.8	4.4	7.4	10.8
	BS	16	...	9.15	20.8	31.1	39.1	41.1	42.2	7.6	10.4	12.4
	MC	38	...	6.84	11.1	18.5	34	41.2	45.3	9.2	11	13.8
	MT	35	...	7.68	20	30.3	33.6	36.2	38.8	11	15.8	18
	Mean	27	...	7.82	17.2	25.8	36.2	40.4	42.3	9.3	11.7	14.2

* Figures in parentheses refer to number of determinations made on each subject.

The mean ventilatory response to carbon dioxide in these subjects is indicated in Figure 7. On this graph the respiratory stimulus is considered as the alveolar CO_2 tension and is plotted on the abscissa. The response, plotted on the ordinate, is the alveolar ventilation ratio (VaR). The calculated alveolar ventilation while the subject is breathing room air during the control period is defined as the alveolar ventilation ratio equal to 1. All other alveolar ventilation ratios are calculated in reference to this value. Thus an alveolar ventilation value which is twice the control alveolar ventilation while breathing room air is expressed as an alveolar ventilation ratio of 2.

The immediate effect of sodium salicylate is to shift the stimulus-response curve to the left but it remains parallel to the control curve. The prolonged action following oral administration of the drug results not only in a further shift to the left but also in a steeper ascent. Since the slope of such a curve $\left(\frac{\Delta VaR}{\Delta P_aCO_2}\right)$ is a quantitative estimate of the ventilation response for any increment in alveolar CO_2 tension (stimulus), it may be regarded as an index of the "sensitivity" of the respiratory center to carbon dioxide. The response of the body to prolonged ingestion of acetylsalicylic acid is to cause a 24 per cent increase in sensitivity of the respiratory center to carbon dioxide (slope constant of ventilation line changes from 0.33 to 0.41), as well as maintained hyperventilation. The absence of change in sensitivity with rapid intravenous administration of salicylate and the further increase in sensitivity on the first day after cessation of the

orally administered drug, in the face of a slight fall in mean blood salicylate level, suggest that this change is not due directly to the salicylate but is the result of secondary changes in blood and tissue attending prolonged hyperventilation. Similar respiratory data have been obtained in

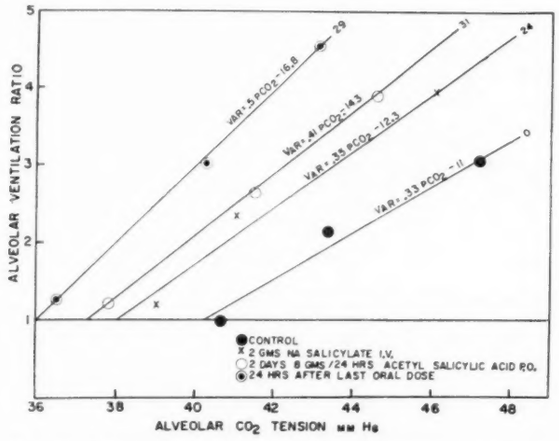

FIG. 7. Mean ventilatory stimulus-response curves to CO_2 in normal man; equations noted are calculated by method of least mean squares and define the lines fitted to mean value points. Data are from Table II or calculated from it (VaR); values at end of line are mean blood salicylate levels for each curve.

three patients receiving prolonged salicylate therapy. The mean alveolar CO_2 tension in this group was 25 mm. Hg and oxygen consumption was increased by 30 per cent. No additional information was added other than to establish that the maintenance of hyperventilation and increase in oxygen consumption is manifest in the presence of disease as well as in health.

Graphic Synthesis of Combined Respiratory Action (Direct and Metabolic). For convenience in quantitating individually the combined effects of salicylate which occur simultaneously in intact animal and man the graph of Figure 8 has been constructed. The simple mathematical relationships of alveolar CO_2 tension, alveolar ventilation and metabolic CO_2 production in the body are portrayed on the major area. Relative values are used, insofar as possible, in order to compare heterogeneous populations as well as to emphasize the generality of these relationships. The abscissa is the tension of CO_2 in the alveolar air. The normal value is arbitrarily selected at 40 mm. Hg. The ordinate represents relative CO_2 production. Whatever the absolute control value, it is represented by 1 on this axis. A similar ordinate is drawn for oxygen consumption but remains valid throughout any experimental procedure only so long as the respiratory gas exchange ratio is the same for any two time periods being compared. If the gas exchange ratio is 0.8 and the absolute value of CO_2 production at the control period is 80 cc. per unit of time, then it is clear that the similar

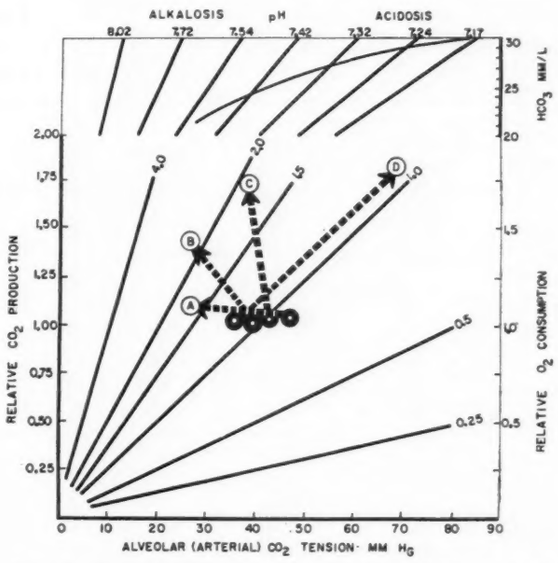

FIG. 8. Graphic representation of interrelation of alveolar CO_2 tension, metabolic CO_2 production and alveolar ventilation (portrayed as family of alveolar ventilation ratio isopleths radiating from origin); solid dots represent mean control alveolar points, and arrows indicate direction of movement of alveolar points in appropriate experiments to arrive at final values indicated by open circles. (See text for interpretation.) A, mean final alveolar point of dogs with pure respiratory stimulation following application of sodium salicylate to fourth ventricle of brain; B, final mean point for normal man receiving prolonged oral salicylate therapy with mean blood level of about 30 mg. per 100 cc.; C, mean final point for anesthetized dogs receiving 100 mg./kg. sodium salicylate intravenously; D, mean final point for curarized dogs receiving 100 mg./kg. sodium salicylate and maintained at constant ventilation in whole body respirator.

point on the oxygen consumption scale, indicated at relative value 1, represents an absolute oxygen consumption value of 100 cc. The only advantage in adding the oxygen consumption ordinate is that thinking is often in terms of this parameter rather than of CO_2 production. Since alveolar CO_2 tension is directly proportional to the level of metabolic CO_2 production, but inversely proportional to the magnitude of alveolar ventilation, alveolar ventilation isopleths may be represented as a family of straight lines radiating from the origin of this plot. Alveolar ventilation ratios are indicated on the

appropriate lines. As the isopleths approach the vertical position the alveolar ventilation ratios converge rapidly to infinity since it is only at infinite ventilation that the alveolar CO_2 tension can remain zero. The normal alveolar point is at 40 mm. Hg alveolar CO_2 tension, relative CO_2 production = 1, and lies on the alveolar ventilation ratio line labelled 1. Pure vertical displacement of the alveolar point represents ventilatory response which is entirely secondary to changes in the level of CO_2 production. Since in this instance the tension of CO_2 in the alveolar air (and arterial blood) remains unaltered, the total respiratory economy of the body is static. On the other hand, ventilatory response of purely nervous origin results in a horizontal displacement of the alveolar point with resultant changes of CO_2 tension and hence in acid-base balance of the body. Combined effects are seen as vectoral resultants of the two "pure" cases cited. All possible variations in salicylate response must fall within the area defined by the extreme vectors determined experimentally (points A and D). Point A represents the final alveolar value from pure central stimulant effect achieved in the dog by topical application of salicylate to the medulla. Point D, on the other hand, is the final alveolar point for a dog whose respiration is maintained at a constant value in a whole body respirator and can exhibit only the effects of salicylate-induced increase in oxygen consumption and carbon dioxide output. The alveolar point can move only up and to the right along the control alveolar ventilation isopleth. It is clear that if the ventilatory response does not keep pace with the increase in CO_2 production, respiratory acidosis develops. The usual effect seen in the lightly anesthetized animal or in man is a combination of the two with a dominant central stimulant action resulting in respiratory alkalosis (points B and C).

TABLE III

RESPIRATORY DATA IN DOGS BEFORE AND AFTER INTRAVENOUS INJECTION OF 100 MG./KG. SODIUM SALICYLATE

Dog	Respiratory Frequency (breaths/min.)	Minute Volume (L./min.)	O_2 Consumption (ml./min.)	P_aO_2 (mm. Hg)	P_aCO_2 (mm. Hg)	Blood pH	Arterial O_2 Content (vol. %)	Arterial CO_2 Content (vol. %)	Venous O_2 Content (vol. %)	Venous CO_2 Content (vol. %)
				Control						
1	9.5	1643	163	96	44.6	7.50	15.9	48.8	11.7	52.4
2	6	1770	148	93	45.7	7.42	13.2	53.3	8.9	55.3
3	5	834	67	100	37.4	7.44	14.0	48.6	11.5	49.9
4	10	1430	85	99.4	41.5	7.41	14.2	45.7	11.3	47.7
5	10	2000	125	99	46.6	7.42	17.1	46.0	13.5	48.6
6	8.5	2978	179	94	45.1	7.47	17.5	49.5	14.3	50.1
7	7	1890	128	104	36	7.41	18.1	44	14.5	47.7
8	24	3504	123	108	35	7.44	12.9	46.5	9.2	....
Mean	10	2006	127	99.1	41.5	7.44	15.36	47.8	11.8	50.2
				25 Minutes after Salicylate						
1	15	3960	329	101	41.7	7.53	15.9	47.2	9.3	52.7
2	5.5	1975	242	.....	46.4	7.47	13.0	48.7	7.4	53.3
3	6.5	1625	103	100	40.5	7.40	14.3	47.7	10.0	51.9
4	13	2600	144	102	40.3	7.45	13.5	44.8	9.8	48.9
5	14	3206	180	95	36.6	7.52	18.6	38.8	13.2	42.3
6	10	4550	320	94	44.4	7.47	17.3	48	12.5	55.2
7	9.5	2907	220	103	37	7.50	15.4	43.1	8.9	50.4
8	27	5606	192	126	20	7.47	15.1	38.1	9.7	44.7
Mean	12.5	3303	216	216	38.3	7.48	15.36	44.6	10.1	49.9

The simultaneous events which take place in the blood during any acute experiment are represented at the top of Figure 8. A range of blood bicarbonate values is indicated in the upper right section. The common alveolar

(arterial) CO_2 tension abscissa allows one to draw a CO_2 dissociation curve which is indicated as the curved line in the figure. pH isopleths are calculated from the Henderson-Hasselbalch equation and are represented by the family of straight lines in this portion of the figure. The arterial point is determined by projecting vertically from the alveolar point until the CO_2 dissociation curve is met. The pH is then read directly. This method is not applicable to chronic experiments in which there may be compensatory excretion of bicarbonate unless one has sufficient data to draw the new dissociation curve.

TABLE IV

CIRCULATORY DATA IN DOGS BEFORE AND AFTER INTRAVENOUS INJECTION OF 100 MG./KG. SODIUM SALICYLATE

Dog	Pulse Rate (beats/min.)	Carotid Pressure (S/D mm. Hg)	Right Ventricular Pressure (S/D mm. Hg)	A-V O_2 diff.	Cardiac Output (L./min.)	Stroke Volume (ml.)
			Control			
1	150	165/126	29.5/1	4.2	3.9	26
2	125	162/120	18/0	4.3	3.45	27.5
3	160	165/125	24/0	2.5	2.48	15.5
4	78	180/138	29.5/0	2.9	2.93	37.5
5	81	167/125	24/0	3.6	3.47	43
6	150	225/175	37/0	3.2	5.60	37.3
7	170	155/110	30/0	3.6	3.55	21
8	145	134/100	31/0	3.7	3.32	23
Mean	133	169/127	27.9/0	3.5	3.59	28.8
			25 Minutes after Salicylate			
1	174	165/130	35/1	6.6	5.00	28.7
2	126	164/128	21/0	5.6	4.32	34.3
3	120	155/120	25/11	4.3	2.40	20
4	78	179/143	29/1	3.7	3.90	50
5	78	174/137	27/0	5.4	3.34	43
6	150	218/175	34/0	4.8	6.66	44
7	182	147/112	31/1	6.5	3.40	18.7
8	180	172/120	42/0	5.4	3.56	19.8
Mean	136	172/133	31/2	5.3	4.07	32.3

Circulatory Adjustments. It is of major interest to know how the body adjusts, in respect to the cardiovascular system, to the increase in oxygen consumption caused by salicylate. Tables III and IV list the data obtained to help answer this question. The low arterial oxygen content noted during the control period, and the wide alveolo-arterial oxygen gradient, are characteristic of dogs under pentobarbital anesthesia.[15] It is noted that about half of the increase in oxygen consumption caused by salicylate is met by widening the arteriovenous oxygen difference but the other half is met only at the expense of increasing cardiac output. This is effected largely by an increase in stroke volume since the pulse rate increases only slightly.

Pressures in both the systemic and lesser circuit increased promptly following intravenous administration of sodium salicylate. Figure 9 illustrates one such experiment. Within fifteen minutes systemic pressure tended to return to the approximate control value, although in one instance it fell below and in one instance (illustrated) it remained above the control level for one hour. The gradual fall in systemic pressure to normal in the presence of an elevated cardiac output suggests peripheral vasodilatation and fall in vascular resistance to flow. This probably is related to the mechanism by which salicylates act to lower body temperature. Right ventricular pressure remained elevated throughout the course of all experiments; the extent of rise could be wholly accounted for on the basis of the increase in pulmonary blood flow.

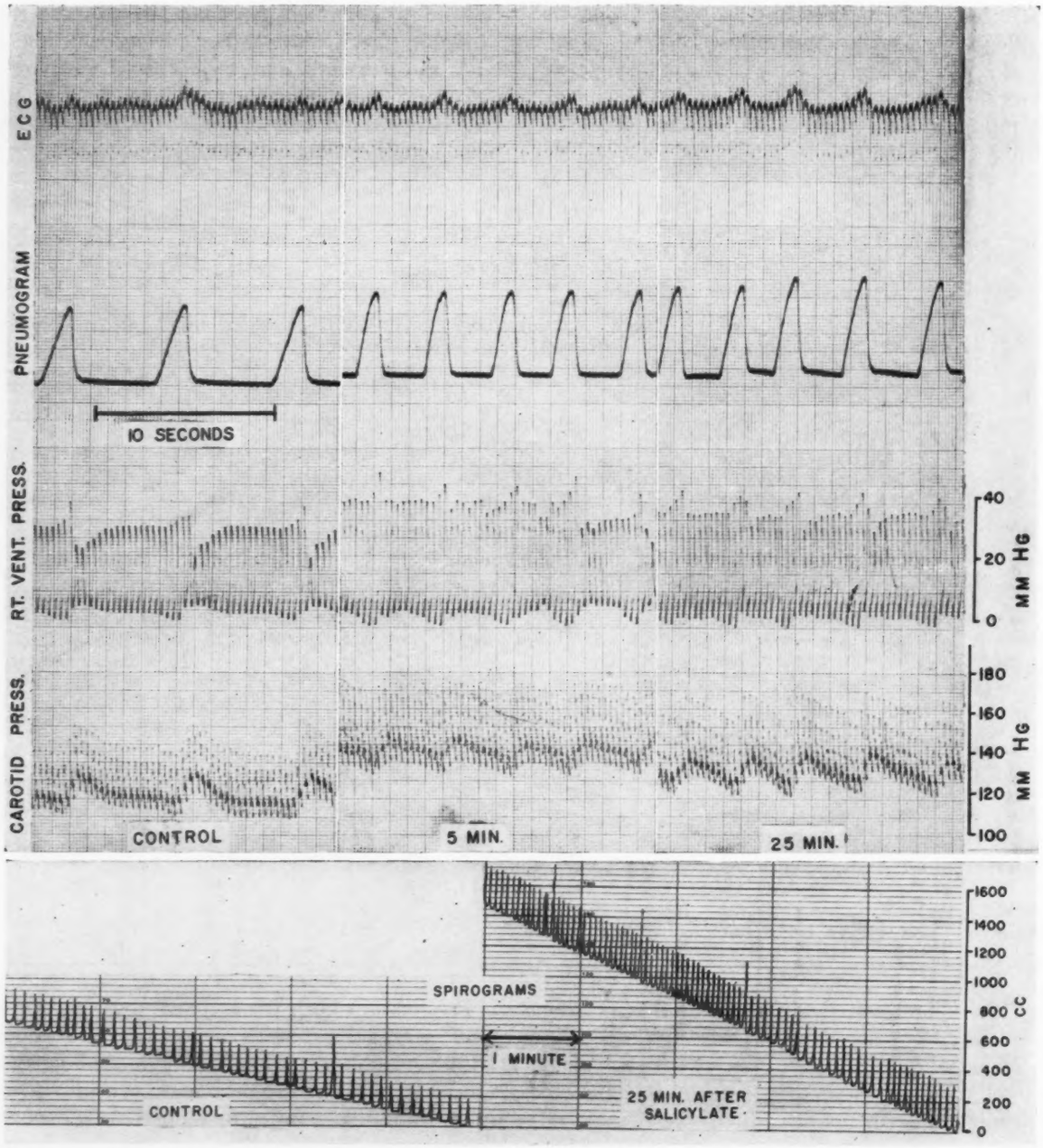

FIG. 9. Representative records of dogs after intravenous injection of 100 mg./kg. sodium salicylate.

The initial pressure response is independent of the release of epinephrine since it occurs under adrenergic blockade (dibenzylene). It is probably independent of nervous influence altogether since the initial response is also seen in the presence of complete ganglionic blockade (tetraethyl ammonium chloride). This is interpreted to mean that salicylate probably has a direct stimulating action on cardiac muscle. In the experiments with tetraethyl ammonium chloride the initial rise in systemic pressure following salicylate was followed much more promptly by a return to the control level than in animals not under the influence of tetraethyl ammonium chloride.

No change in the electrocardiogram was observed in these experiments.

A comprehensive summary of the respiratory

and circulatory changes listed in or derived from Tables III and IV is portrayed in Figure 10.

COMMENTS

The early clinical reports which indicated a metabolic stimulating effect of salicylate made little comment on this response.[9] More recent studies have raised the interesting speculation as to whether the therapeutic actions of salicylates may in some way be related to the rise in tissue oxygen consumption.[10,13] Little attention has been given to the major effect that the change in respiratory gas metabolism may have on the interpretation of both the respiratory response and the ultimate change in acid-base balance. There is no clue to the biochemical mechanism by which this stimulation is mediated, although the similarity of the dinitrophenol effect has been pointed out.[13]

The change in sensitivity of the respiratory center is not surprising since this altered state is readily observed in other situations of chronic hyperventilation, whether it is caused by prolonged hypoxia[16] or mechanical hyperventilation.[17] The order of change coincides well with general predictions concerning alterations in CO_2 and bicarbonate discussed elsewhere.[18]

The present series of experiments confirms the more recent view that in adult man respiratory alkalosis is the anticipated alteration in acid-base balance associated with the effects of salicylate.[8] The older studies purporting to show a metabolic acidosis are almost certainly the result of faulty interpretation of blood CO_2 combining power values. The fatal effects of salicylate during the terminal period require further clarification, but the older studies demonstrating a late fall in blood pH in the experimental animal may very likely be related to an acidosis which is not metabolic in the sense in which this term is ordinarily employed. If for any reason the ventilatory mechanism fails to keep pace with the increase in CO_2 production secondary to salicylate stimulation of metabolism, an acidosis results. It is, however, a respiratory acidosis since it must invariably be associated with a rise in alveolar (and arterial) CO_2 tension without a fall in plasma bicarbonate.

The circulatory effect raises the interesting question as to whether, with large doses of salicylate, cardiac output also is increased. This would be of particular importance in such states as rheumatic carditis. A direct action upon the heart has been sought in isolated tissue work in the past but no consistent changes have been noted. High concentrations may be directly depressant, but lower concentrations have a stimulating effect on rate and amplitude of contraction.[19,20] A rise in systemic blood pressure has been noted in the past even in the face of vasodilatation.[21,22]

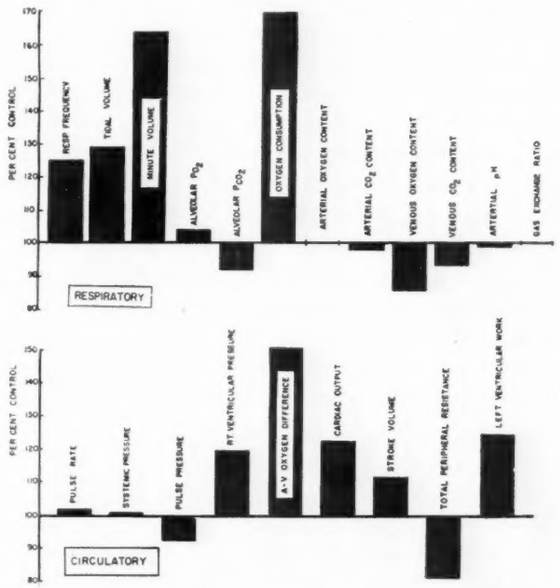

FIG. 10. Mean changes in respiratory and circulatory measurements plotted as per cent of control value, following intravenous injection of 100 mg./kg. sodium salicylate. Estimates calculated from data of Tables III and IV.

SUMMARY

1. Sodium salicylate has a direct respiratory stimulant action. The locus of this effect is in the medulla and is independent of the aortic and carotid chemoreceptor areas.

2. Sodium salicylate also is a profound metabolic stimulant and may increase oxygen consumption two-fold. A dosage-response relationship has been established in dogs, the maximum effect being noted at dosages of about 100 mg./kg. when the drug is given intravenously. The source of metabolic increase is primarily skeletal muscle and is independent of the central and peripheral nervous system. It is also not dependent on epinephrine release.

3. In normal man prolonged salicylate administration increases the "sensitivity" of the respiratory center to carbon dioxide.

4. The principal change in acid-base balance in the intact dog and adult human is the development of respiratory alkalosis. When ventilation is inadequate, respiratory acidosis may

develop. A diagram is presented to illustrate and differentiate the combined actions of salicylate on the respiratory mechanism—direct stimulation and secondary stimulation via increase in level of metabolism.

5. The circulatory system meets the increased level of oxygen consumption by widening the auriculoventricular oxygen difference and increasing cardiac output. There is an initial rise in systemic pressure, which usually returns to normal within fifteen minutes. Right ventricular pressure rises early and remains high for at least one hour. The magnitude of rise is directly proportional to the increase in cardiac output. The initial pressure rise is not caused by epinephrine release and can also be demonstrated in the presence of ganglionic blockage (tetraethyl ammonium chloride). It is concluded that this is a direct cardiac muscle effect of salicylate.

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Effect of Salicylate on the Acid-Base Equilibrium of Patients with Chronic CO_2 Retention Due to Pulmonary Emphysema*

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A FEW years ago it was demonstrated that salicylate may induce respiratory alkalosis in animals and humans[1–3] and recently it was shown that salicylate increases hyperventilation induced by CO_2 inhalation in normal human subjects.[4] Therefore it seemed logical to investigate the effects of salicylate in patients with chronic retention of CO_2 due to pulmonary emphysema.

METHODS

Patients with chronic CO_2 retention due to pulmonary emphysema without evidence of acute or recent respiratory infection were studied under basal conditions.

A first series of observations was designed to study acute effects of sodium salicylate on the acid-base equilibrium of the blood of patients breathing room air. After a control period, 6 to 8 gm. of sodium salicylate dissolved in 250 to 300 cc. of isotonic sodium chloride solution were administered intravenously over a period of forty-seven to sixty-seven minutes. Samples of arterial blood were collected anaerobically from the brachial artery through an indwelling needle at appropriate intervals during the control period and after the administration of salicylate. Heparin was used as anticoagulant, and blood samples were analyzed immediately. Whole blood pH was measured with a Beckmann model G pH-meter at room temperature and corrected to body temperature value.[5] Arterial plasma CO_2 content and arterial blood oxygen content and capacity were determined by the methods of Van Slyke and Neill.[6,7] Plasma CO_2 tension was calculated from the Henderson-Hasselbalch equation. The plasma salicylate level was determined by the method of Coburn.[8]

In a second series of experiments the patients breathed room air during the control period. After the control period they breathed pure oxygen administered by mask for thirty-five to ninety minutes; then the acute effects of the intravenous administration, over a forty to sixty-five minute period, of 6 to 8 gm. of sodium salicylate dissolved in 300 to 500 cc. of isotonic sodium chloride solution were observed while the patients continued to inhale pure oxygen. Samples of blood were collected, as in the first series of experiments, during the control period and during the period of oxygen inhalation before and after administration of salicylate. Blood pH, plasma CO_2 content, blood oxygen content and capacity and plasma salicylate were determined as in the first series of experiments.

The third series of observations dealt with the effects of acetylsalicylic acid administered orally over a period ranging from three to twenty-two days. After a control period patients were given approximately 0.6 to 1.8 gm. of aspirin every six hours, day and night. Blood samples were collected anaerobically at the same time of day, the patients being in a basal state. In some experiments arterial blood was collected and analyzed as in the first two series of experiments; in other experiments only venous blood drawn from the antecubital vein without stasis was analyzed; in some experiments both

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venous blood and an occasional arterial blood sample were analyzed. Blood samples were always drawn just before the administration of a dose of aspirin.

RESULTS

The results observed are summarized in Tables I, II and III.

A. Acute effects of intravenous administration of sodium salicylate. As can be seen in Table I, five patients received 6 to 8 gm. of sodium salicylate intravenously within forty-seven to sixty-seven minutes. The maximal plasma salicylate levels noted occurred three to ninety-two minutes after termination of the salicylate injection and ranged from 21.1 to 51.9 mg. per

TABLE I

EFFECT OF INTRAVENOUS ADMINISTRATION OF SODIUM SALICYLATE ON ARTERIAL BLOOD pH, pCO_2, BICARBONATE AND OXYGEN SATURATION IN PATIENTS WITH ANOXEMIA AND HYPERCAPNIA DUE TO CHRONIC PULMONARY EMPHYSEMA

Observation Number	Patient, Age	Time (min.)	Arterial Blood pH	Arterial Plasma pCO_2 (mm. Hg)	Arterial Plasma HCO_3^- (mEq./L.)	Plasma Salicylate (mg. %)	Arterial Blood Oxygen Saturation (%)
1	H. W., 64	− 57	7.33	82	42.0	0	69.7
		− 5	7.32	81	40.7	0	.....
		0 to +60	Infusion of 6 gm. of sodium salicylate dissolved in 300 cc. of isotonic sodium chloride solution				
		+ 63	7.35	78	41.7	21.1	76.8
		+123	7.35	73	38.9	20.8	80.2
		+188	7.38	64	36.7	....	91.8
		+263	7.35	72	38.5	14.8	71.8
2	F. B., 63	− 25	7.34	68	35.7	0	79.5
		− 5	7.33	69	35.4	....	79.5
		0 to +47	Infusion of 6 gm. of sodium salicylate dissolved in 300 cc. of isotonic sodium chloride solution				
		+ 79	7.39	58	34.2	25.0	85.0
		+139	7.40	56	33.9	26.5	83.0
		+195	7.43	53	34.1	21.1	80.0
3	J. H., 63	− 30	7.34	59	31.0	....	.....
		− 5	7.32	62	30.9	0	80.4
		0 to +60	Infusion of 8 gm. of sodium salicylate dissolved in 300 cc. of isotonic sodium chloride solution				
		+ 80	7.33	60	30.6	26.6	90.4
		+135	7.36	54	29.7	25.0	.....
		+195	7.42	46	29.1	23.5	93.6
		+220	7.43	44	28.5	22.2	90.4
4	C. F., 64	− 15	7.33	60	30.4	0	77.8
		− 5	7.33	61	31.2	0	75.8
		0 to +67	Infusion of 8 gm. of sodium salicylate dissolved in 300 cc. of isotonic sodium chloride solution				
		+ 82	7.41	49	30.3	51.9	83.1
		+130	7.43	46	29.8	47.2	86.2
		+175	7.38	51	29.3	44.7	77.4
		+210	7.38	50	28.4	41.6	75.0
5	X. A., 62	− 13	7.27	73	32.7	0	17.8*
		− 8	7.29	69	32.0	0	18.2*
		0 to +60	Infusion of 8 gm. of sodium salicylate dissolved in 250 cc. of isotonic sodium chloride solution				
		+ 80	7.37	55	30.8	23.4	18.5*
		+135	7.41	49	30.0	24.5	19.2*
		+185	7.43	45	29.1	23.5	19.8*

* Arterial blood oxygen content (vol. %).

cent. The administration of salicylate resulted in a decrease of plasma pCO_2, the maximal decrease being reached from sixty-three to one hundred and sixty minutes after the end of the infusion. The plasma pCO_2 was still markedly depressed when the observations were discontinued, as long as 203 minutes after cessation of the salicylate administration. The arterial blood pH rose, the maximal rise coinciding with the maximal decrease in the plasma pCO_2. The plasma bicarbonate decreased. The oxygen content and saturation of the arterial blood rose in four of the five patients; in the remaining patient, in whom only the oxygen content of the arterial blood was measured, the oxygen content rose as in the other four patients.

B. Acute effects of the intravenous administration of sodium salicylate during inhalation of pure oxygen. As can be seen in Table II, five experiments were performed on four patients. In all five observations administration of pure oxygen by mask resulted in a rise in plasma pCO_2 as well as in oxygen content and saturation of the arterial blood and decrease in plasma pH. The plasma bicarbonate rose slightly but consistently. With inhalation of pure oxygen continued, 6 to 8 gm. of sodium salicylate dissolved in 300 to 500 cc. of isotonic sodium chloride solution were administered intravenously. The plasma salicylate level reached a maximum ranging from 20.0 to 26.3 mg. per cent. In all five experiments (except in the first of the two observations made on patient F. B., Table II) administration of sodium salicylate resulted in decrease of the plasma pCO_2 towards, to or below its level before oxygen inhalation was begun, and a rise of the blood pH towards or above its value before initiation of oxygen inhalation. The maximal effect was reached 20 to 125 minutes after the end of the salicylate infusion but some effect persisted 115 to 125 minutes after the end of the infusion. The oxygen content and saturation of the arterial blood remained essentially unchanged by administration of salicylate. In the first observation made on patient F. B. (Observation 2 of Table II), in which the salicylate blood level was the lowest in this series of experiments, the plasma pCO_2 and pH did not change after the salicylate injection. However, it is probable that even at such a low salicylate level a further rise in pCO_2 and decrease in pH during the continued inhalation of oxygen was obviated as is indicated by the fact that, as the salicylate level began to decrease, the pCO_2 rose further and the pH fell. Furthermore, as can be seen in Table II, the same patient, F. B., responded to the salicylate injection as did the other patients when, during a second experiment (Observation 3 of Table II) performed fourteen days after the first experiment, a higher blood salicylate level was obtained by administration of 8 gm. instead of 6 gm. of sodium salicylate.

C. Effects of continued administration of aspirin by mouth. The results observed are summarized in Table III. Four patients, H. W., F. B., B. L. and C. F., reacted in a similar manner. In Observation 1 patient H. W. was given 1.5 gm. of aspirin every six hours for six days. On the sixth day of aspirin administration the plasma salicylate level was 16 mg. per cent. In Observation 2 patient F. B. was given 2 gm. of aspirin every six hours for one day, than 2 gm. every eight hours for two days. In Observation 3 patient B. L. received 1.8 gm. of aspirin every eight hours for nine days, and the plasma salicylate level ranged between 16.5 and 22.6 mg. per cent. In Observation 4 patient C. F. was given 0.9 gm. of aspirin every eight hours for five days, then 0.6 gm. every six hours for four days, and the plasma salicylate level ranged between 22.8 and 30.7 mg. per cent.

In the first two observations the administration of aspirin resulted in a decrease of arterial plasma pCO_2 and bicarbonate and a rise in the arterial blood pH. In patients B. L. and C. F. the total CO_2 of the venous plasma fell progressively. When administration of aspirin was discontinued after six, three and nine days, respectively, in patients H. W., F. B. and C. F., arterial plasma pCO_2 and bicarbonate, as well as the arterial blood pH, or the venous plasma CO_2 returned toward, to or even beyond control levels. In Observation 5 patient L. B. received 1.8 to 2.4 gm. of aspirin every eight hours and the plasma salicylate levels ranged between 21 and 40.3 mg. per cent. In this patient, only the higher concentrations of salicylate in the blood were associated with a significant fall in the total CO_2 of the venous plasma. Finally, in Observation 6 patient H. W., who had responded previously to oral administration of 6 gm. of aspirin per day (Observation 1), did not respond at all to the administration of a dose of aspirin slightly larger than that given in Observation 1. Whether or not this lack of response was related to the upper respiratory infection which the patient was noted to have on the seventh day of aspirin administration cannot be determined.

TABLE II

EFFECT OF INTRAVENOUS SODIUM SALICYLATE DURING INHALATION OF 100% OXYGEN ON ARTERIAL BLOOD pH, pCO_2, BICARBONATE AND OXYGEN SATURATION IN PATIENTS WITH ANOXEMIA AND HYPERCAPNIA DUE TO CHRONIC PULMONARY EMPHYSEMA

Observation Number	Patient, Age	Time (min.)	Arterial Blood pH	Arterial Plasma pCO_2 (mm. Hg)	Arterial Plasma HCO_3^- (mEq./L.)	Plasma Salicylate (mg. %)	Arterial Blood Oxygen Saturation (%)
1	H. W., 64	−114	7.39	69	40.6	....	79.2
		− 94	7.39	68	39.8	....	77.4
		− 90 Beginning of inhalation of 100% oxygen by mask					
		− 35	7.28	92	41.7	....	100
		− 4	7.26	96	41.7	0	97.5
		0 to +65 Infusion of 6 gm. of sodium salicylate dissolved in 500 cc. of isotonic sodium chloride solution					
		+ 95	7.31	86	42.1	26.3	100
		+140	7.32	82	41.1	25.0	100
		+190	7.34	76	39.7	23.5	100
2	F. B., 63	− 95	7.38	59	33.7	0	80.2
		− 75	7.39	58	34.2	....	75.2
		− 65 Beginning of inhalation of 100% oxygen by mask					
		− 30	7.32	72	35.8	0	100
		− 2	7.31	75	36.5	0	100
		0 to +40 Infusion of 6 gm. of sodium salicylate dissolved in 300 cc. of isotonic sodium chloride solution					
		+ 68	7.31	74	36.1	20.0	100
		+125	7.31	75	36.5	19.0	98.8
		+182	7.31	75	36.4	....	100
		+213	7.28	78	35.3	18.7	84.9
3	F. B., 63	− 60	7.35	54	29.2	....	90.4
		− 50	7.37	52	29.3	....	85.8
		− 45 Beginning of inhalation of 100% oxygen by mask					
		− 30	7.25	72	30.4	....	98.7
		− 4	7.24	76	31.6	0	100
		0 to +45 Infusion of 8 gm. of sodium salicylate dissolved in 300 cc. of isotonic sodium chloride solution					
		+ 75	7.34	60	31.2	25.0	100
		+120	7.31	63	30.9	23.5	.....
		+160	7.28	69	31.5	23.0	100
4	L. B., 61	− 45	7.35	63	33.5	....	85.0
		− 40	7.36	61	33.6	....	87.6
		− 35 Beginning of inhalation of 100% oxygen by mask					
		− 16	7.28	76	34.8	....	.....
		− 5	7.28	77	35.3	0	99.6
		0 to +50 Infusion of 8 gm. of sodium salicylate dissolved in 300 cc. of isotonic sodium chloride solution					
		+ 70	7.37	63	35.2	25.0	100
		+125	7.36	65	35.2	24.5	.....
		+174	7.34	65	34.4	24.4	94.6
5	D. F., 61	− 69	7.38	54	31.6	....	92.5
		− 64	7.38	54	31.7	....	89.4
		− 60 Beginning of inhalation of 100% oxygen by mask					
		− 34	7.33	64	32.8	....	.....
		− 10	7.32	65	32.4	0	100
		0 to +50 Infusion of 8 gm. of sodium salicylate dissolved in 300 cc. of isotonic so dium chloride solution					
		+ 65	7.37	54	30.4	24.2	100
		+115	7.39	51	29.8	24.0	.....
		+165	7.38	52	29.8	22.3	.....

TABLE III

EFFECT OF ORAL ADMINISTRATION OF ASPIRIN ON ARTERIAL BLOOD pH, pCO_2 AND BICARBONATE AND/OR TOTAL CO_2 CONTENT OF THE VENOUS BLOOD IN PATIENTS WITH ANOXEMIA AND HYPERCAPNIA DUE TO CHRONIC PULMONARY EMPHYSEMA

	Time (days)	Arterial Blood pH	Arterial Plasma pCO_2 (mm. Hg)	Arterial Plasma HCO_3^- (mEq./L.)	Plasma Salicylate (mg. %)	Venous Plasma Total CO_2 (mEq./L.)
Observation 1	− 4	7.28	67	30.8	....	....
Patient H. W. (64 yr.)	− 1	7.35	58	30.8	....	....
	0	Administration of aspirin started, 6 gm. orally daily				
	+ 3	7.40	44	26.3	....	....
	+ 5	7.40	40	24.3	16.0	....
	+ 6	Administration of aspirin stopped				
	+ 9	7.31	68	33.2	....	....
Observation 2	− 1	7.28	66	30.0	....	....
Patient F. B. (63 yr.)	0	Administration of aspirin started, 8 gm. orally daily				
	+ 1	Aspirin reduced to 6 gm. orally daily				
	+ 3	7.36	46	25.4	....	....
	+ 3	Administration of aspirin stopped				
	+ 6	7.32	56	27.8	....	....
Observation 3	− 1	....	..	....	....	31.2
Patient B. L. (59 yr.)	0	Administration of aspirin started, 5.4 gm. orally daily				
	+ 1	....	..	....	....	30.7
	+ 5	....	..	....	22.6	28.5
	+ 6	....	..	....	16.5	30.0
	+ 7	....	..	....	22.6	28.9
	+ 8	....	..	....	21.6	27.0
Observation 4	− 2	....	..	....	....	36.3
Patient C. F. (64 yr.)	0	....	..	....	....	37.4
	0	Administration of aspirin started, 2.7 gm. orally daily				
	+ 2	....	..	....	22.8	35.6
	+ 4	....	..	....	30.7	30.6
	+ 5	Aspirin reduced to 2.4 gm. orally daily				
	+ 6	....	..	....	24.2	31.9
	+ 9	Administration of aspirin stopped				
	+ 9	....	..	....	10.5	39.3
	+11	....	..	....	0	41.2
	+13	....	..	....	....	40.7
Observation 5	− 1	....	..	....	....	42.0
Patient L. B. (61 yr.)	0	....	..	....	....	43.8
	0	Administration of aspirin started, 7.2 gm. orally daily				
	+ 3	....	..	....	40.3	36.5
	+ 4	Aspirin reduced to 5.4 gm. orally daily				
	+ 5	....	..	....	34.0	40.5
	+ 7	....	..	....	28.6	40.8
	+10	....	..	....	21.0	43.1
	+11	Aspirin increased to 6.3 gm. orally daily				
	+13	....	..	....	26.8	41.7
Observation 6	− 2	7.38	57	32.6	0	....
Patient H. W. (64 yr.)	0	7.38	59	34.0	....	....
	0	Administration of aspirin started, 6.9 gm. orally daily				
	+ 4	7.38	53	30.5	20.0	....
	+ 7	7.36	60	33.0	20.0	....
	+11	7.39	54	31.9	20.0	....
	+15	7.37	55	30.9	19.7	....
	+22	7.31	76	37.0	19.0	....

In one patient not included in Table III oral administration of aspirin was begun six hours after completion of Observation 5 noted in Table II. This experiment, intended to study the effect of prolonged aspirin administration, could not be continued because of the development of an acute psychosis on the second day of oral administration of aspirin. At this time the plasma salicylate level was 41.8 mg. per cent. Administration of aspirin was discontinued and within twenty-four hours, at which time the plasma salicylate concentration was 26.2 mg. per cent, the psychosis cleared completely. Most patients became irritable during the acute and prolonged experiments involving salicylate administration. Two patients developed coarse tremor of the hands during the period of oral administration of aspirin.

COMMENTS

It is now well established that salicylate stimulates the respiratory center in animals and men.[1–4] However, the exact site of the stimulation is still not definitely known. Some authors[9] believe that salicylate stimulates the respiratory center both directly and via the sinoaortic nerves, whereas others[10] are of the opinion that stimulation of the respiratory center is only reflex in nature. Furthermore, the precise *modus operandi* of this stimulation is also unknown, although Alexander, Spalter and West[4] believe that at least one mechanism whereby salicylate acts on the respiratory center is that of sensitizing it to CO_2. Whatever the answer to these questions may be, it seems clear from our first series of experiments that, just as in normal animals or humans, salicylate can lower the arterial pCO_2 and raise the arterial pH in patients who retain CO_2 because of emphysema and because they seem to have become insensitive to CO_2. Although no direct measurements of pulmonary ventilation were made in the experiments described in this paper, hyperventilation was observed in the patients after intravenous administration of salicylate, and there is no doubt that the immediate effects of salicylate on the acid-base equilibrium are largely explained by the increase in pulmonary ventilation. It is of interest that salicylate lowers the arterial blood pCO_2 and raises the arterial blood pH, although by increasing the pulmonary ventilation it tends to correct the anoxemia which in such patients has become a potent respiratory drive.

A more direct demonstration of this property of salicylate was provided by the second series of experiments. It has been known for some time that in patients with emphysema who have become anoxemic and hypercapnic correction of the anoxemia by administration of oxygen intensifies hypercapnia and may result eventually in coma.[11,12] In the second series of experiments salicylate proved effective in reducing accumulation of CO_2 which had been induced by administration of oxygen. It would, of course, be of great interest to compare the efficacy of salicylate with that of the more conventional respiratory analeptics.

The third series of experiments demonstrated that oral administration of aspirin can reduce the retention of CO_2 and keep the blood pCO_2 depressed for as long as the administration of aspirin is continued, at least within the limits of duration of the present observations. However, only four of the six patients studied responded to a moderate dose of aspirin. One patient responded only to a rather large dose of the drug, and one patient who had reacted to a moderate dose of aspirin subsequently did not respond to a slightly larger dose.

Obviously study of a larger series of patients is necessary to permit a definite conclusion as to the efficacy of aspirin to lower and keep within the normal range the pCO_2 of patients with CO_2 retention due to chronic pulmonary emphysema. It must be remembered that collection of valid data on the prolonged administration of aspirin is difficult because the degree of CO_2 retention may fluctuate widely and rapidly with variations in the degree of bronchial obstruction, especially if a respiratory infection occurs. It should be pointed out that the doses of aspirin used caused irritability, occasionally coarse tremor of the hands and, on one occasion, temporary psychosis. Such side effects would seem to have been more marked in this group of patients than in a group of much younger patients who received similar or higher doses of aspirin for acute rheumatic fever.[13]

Whether the use of salicylate as a relatively long-acting respiratory stimulant will prove of therapeutic value remains to be determined by further work. The experience herein recorded suggests that it may be a useful adjunct in the treatment of patients with pulmonary emphysema in whom concurrence of severe anoxemia and hypercapnia makes administration of oxygen both a necessity and a hazard.

SUMMARY

In patients with chronic pulmonary emphysema which has led to anoxemia and hypercapnia it has been observed that: (1) The intravenous administration of 6 to 8 gm. of sodium salicylate over a period of approximately one hour lowers the arterial plasma pCO_2, raises the arterial blood pH and increases the arterial blood oxygen saturation. (2) When inhalation of oxygen has led to aggravation of hypercapnia, intravenous administration of 6 to 8 gm. of sodium salicylate over a period of approximately one hour reduces the degree of hypercapnia. (3) The oral administration of 3 to 7 gm. of aspirin per day in divided doses over a period of a few days gives variable results. In some patients relatively low plasma salicylate levels reduce the hypercapnia, in others only rather high levels are effective, in still others even such high levels are ineffective.

The therapeutic implications of these observations on the effect of salicylate in patients with chronic pulmonary emphysema, anoxemia and hypercapnia are pointed out but they must remain mere implications until more data are accumulated.

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Respiratory and Renal Effects of a Carbonic Anhydrase Inhibitor (Diamox) on Acid-Base Balance in Normal Man and in Patients with Respiratory Acidosis*

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INTEREST in the effect of carbonic anhydrase inhibition on the liberation of carbon dioxide from red blood cells in the pulmonary alveolar capillaries and on pulmonary ventilation has recently been stimulated by the introduction of diamox® (2 acetylamino-1-3,4 thiadiazole-5-sulfonamide), a potent inhibitor of this enzyme.[1] Roughton observed that sulfanilamide, a considerably less potent carbonic anhydrase inhibitor than diamox, interferes with the release of carbon dioxide in the lungs only during exhausting exercise.[2] This was also noted in recent studies with diamox.[3,4] It was also observed that sulfanilamide causes a consistent fall in the carbon dioxide content of serum.[5–7] The sequence of events leading to this has been debated. Beckman et al. believed that the drug brings about a primary renal loss of bicarbonate (metabolic acidosis) which quickly stimulates compensatory hyperventilation in an attempt to raise the level of arterial blood pH to normal.[8] Hartmann et al. reported that the primary event is ventilatory stimulation resulting in respiratory alkalosis and that subsequent increased renal excretion of bicarbonate was a compensatory attempt to adjust for the rise in arterial blood pH.[9] Since these studies with sulfanilamide were carried out the importance of carbonic anhydrase in the H^+—Na^+ ion exchange mechanism of the renal tubules which conserves fixed base has been demonstrated.[10]

The investigations of Nadell in normal subjects and in patients with respiratory acidosis confirmed the primary renal effects of diamox.[11] She noted a prompt fall in the level of plasma carbon dioxide content and arterial pH, followed by a delay of one to two weeks in the onset of a fall in arterial pCO_2, presumably as a result of respiratory stimulation, and a rise in arterial pH to normal values. This sequence of adjustments seemed unusual and stimulated our interest, particularly since Nadell did not carry out respiratory and gas exchange measurements.

It seemed essential to study the interrelationships of pulmonary ventilation, respiratory gas exchange, acid-base balance, blood electrolyte levels and renal electrolyte excretion rates in order to delineate the readjustments to the metabolic derangements induced by diamox. Such studies carried out in patients with chronic pulmonary emphysema and respiratory acidosis and in patients without lung, heart and kidney disease should contribute to an understanding of the action of the drug, help in the selection of patients who might benefit from its use and point out its limitations and possible contraindications.

The studies of Barach[12] suggested that intensification of acidosis following diamox ingestion due to a loss of plasma bicarbonate might predispose patients suffering from chronic

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emphysema associated with respiratory acidosis to develop carbon dioxide narcosis during oxygen inhalation. On the other hand, the studies of Comroe et al.[13] suggested that should a fall in arterial pCO_2 to 50 mm. Hg or less accompany a decrease in plasma bicarbonate in such patients, they might no longer exhibit a tendency to develop this complication. The variation in response to diamox noted among our patients suffering from chronic pulmonary emphysema associated with respiratory acidosis made it possible to evaluate both these concepts concerning the regulation of respiration.

TABLE 1

MEASUREMENTS OF SOME ASPECTS OF PULMONARY FUNCTION

Patient	Age and Sex	Total Lung Capacity		Residual Volume / Total Lung Capacity (%)	Vital Capacity		Maximum Breathing Capacity		Oxygen Saturation of Arterial Blood (%)
		ml.	% Predicted		ml.	% predicted	L./min.	% predicted	
A. Patients with Chronic Pulmonary Emphysema									
M. A.	64, M	5326	104	57	3180	90	43	48	79
B. M.	53, F	4533	122	69	1710	66	26	42	94
H. R.	51, M	5651	100	70	1940	50	24	21	63
J. T.	68, M	....	...	..	1310	42	22	28	65
J. W.	63, M	3647	70	46	2800	78	28	30	62
B. Patients without Lung, Heart or Kidney Disease									
C. B.	47, M	6023	115	30	4535	112	191	166	96
H. B.	69, M	6017	120	40	3580	103	87	98	95
A. F.	59, M	5715	109	43	3465	95	100	99	95
J. N.	60, M	5437	110	53	2540	74	82	76	96
L. S.	78, M	4208	96	31	2885	95	85	107	94

METHODS

Studies were carried out in a group of five patients with chronic pulmonary emphysema associated with respiratory acidosis and in another group of five patients without lung, heart or kidney disease.

Three of the patients (J. T., J. W., H. R.) in the chronic emphysema group (Table 1) exhibited electrocardiographic changes and x-ray findings compatible with cor pulmonale. Patient J. T. suffered from congestive heart failure, which was poorly controlled by a low-salt diet, digitalis, mercurial diuretics, ammonium chloride and aminophylline. Prior to hospitalization patient J. W. exhibited congestive heart failure, which was controlled by a low-salt diet and digitalis. Signs of congestive heart failure did not recur upon withdrawal of digitalis while in the hospital. Patient H. R., who had suffered from bronchial asthma since childhood, received only subcutaneous injections of adrenalin® when necessary for relief from acute asthmatic attacks for the duration of the study. Studies were carried out only when he had not experienced an asthmatic attack for several days. Patient B. M. had a complicating bronchiectasis. All except patient H. R. expectorated about 1 to 3 ounces of non-foul, mucoid sputum containing clumps of green and yellow matter. All patients studied ate the usual hospital diet except J. T. and J. W., who received a low-salt diet.

Studies were generally begun at about 8 A.M. with the patient in a basal state. To avoid possible variations in pulmonary ventilation due to posture, the head of the bed was raised to the same semi-reclining angle for each patient in every study. At the start of a study the patient voided and this urine was discarded. An indwelling arterial needle was then inserted into the lumen of the right brachial artery under local anesthesia with 2 per cent procaine

hydrochloride. With noseclip and mouthpiece in place, the patient inspired through one arm of a two-way valve and expired through another into a Tissot spirometer of 100 L. capacity. The dead space of the valve and mouthpiece was 55 ml. Tidal volume, respiratory rate and minute volume of respiration were recorded on a constant speed ink-recording drum attached to the spirometer.

Several two-minute respiratory periods were recorded over the next one-half to one hour. An arterial blood sample was then collected anaerobically, using heparin solution as an anticoagulant, during the middle of a seven-minute period of expired air collection. In the early phase of the studies only one arterial blood sample was drawn in a similar manner two to three hours after a dose of the drug. Later, the protocol was changed so that following the preliminary period of registration of respiration arterial blood was drawn just before the ingestion of a dose of diamox and two and four hours thereafter.

Urine was voided under oil immediately after each blood collection, followed by registration of the rectal temperature. In the intervals between blood collections, respirations were recorded and expired air collected during two minutes out of nearly every ten to fifteen minutes. Pulse rate and arterial blood pressure were also recorded at frequent intervals throughout each study.

Duplicate samples of expired air collected during the periods of blood withdrawal and a composite sample of air collected in the two-minute periods in the intervals between blood collections were analyzed for oxygen and carbon dioxide contents in a 0.5 ml. micro-Scholander gas analyzer.[14] The rate of oxygen consumed and carbon dioxide expired per minute and the respiratory exchange ratio (R.Q.) were calculated in the usual manner. All expired volumes in this and in the other ventilatory studies (Table I) were corrected to 37°C. saturated with water vapor and 760 mm. Hg (BTPS). Oxygen consumption and carbon dioxide output are expressed at 0° 760 mm. Hg (STPD).

Arterial blood oxygen and carbon dioxide contents[15] and arterial blood hemoglobin oxygen capacity[16] were analyzed in a Van Slyke manometric apparatus. Arterial pH was measured at room temperature with a sealed glass microelectrode in a model G Beckman pH meter and corrected to 37°C. using the factor of 0.014 per degree.[17] Arterial pCO_2 and plasma bicarbonate were calculated by the Henderson-Hasselbach equation. Plasma and urine sodium and potassium concentrations were analyzed in an internal standard flame photometer,[18] and urinary and plasma chloride concentrations by the method of Wilson and Ball.[19] Urine pH was measured with a sealed glass microelectrode in a Beckman model G pH meter and expressed at room temperature, 25°C. Urine carbon dioxide content was measured according to the method of Van Slyke and Neill.[15]

Residual air volume was measured by the method of Darling, Cournand and Richards[20] with modifications as previously published.[21] This, together with the vital capacity, measured the total lung volume. Vital capacity and maximum breathing capacity were measured in a Collins ventilometer. They represent the maximum volumes attained in a series of three observations at one sitting in a day. The patients had previously been trained in the performance of these tests. The results of these different measurements are summarized in Table I.

RESULTS

Immediate Effects of a Single Dose of Diamox in Patients with Pulmonary Emphysema and Elevated Arterial pCO_2 and in Patients without Lung, Heart or Kidney Disease. The major aspects of the results of studies carried out over four hours following a single dose of diamox in both groups of patients are summarized in Table II. All patients exhibited a prompt fall in plasma bicarbonate level and alkalinization of the urine associated with a diuresis of sodium and, to a lesser extent, of potassium bicarbonate, rarely with chloride ions. Data not included in Table II indicate that nearly all of the immediate electrolyte alterations may occur within one to two hours. The intensity of these responses varied considerably among the different patients. It was not related to the size of the dose of diamox, the initial level of plasma bicarbonate, arterial blood pCO_2, pH or oxygen saturation.

The level of arterial pCO_2 either remained unchanged, fell moderately (4 to 8 mm. Hg) or rose as much as 7 mm. Hg. (Table II.) Arterial pH either remained unchanged or fell as much as 0.07 units, reflecting the combined effects in each instance of the relative changes in arterial pCO_2 and plasma bicarbonate. The level of plasma chloride did not consistently rise as

TABLE II*

IMMEDIATE RESPONSE TO A SINGLE DOSE OF DIAMOX

Patient	Dose (mg./kg.)	Plasma		Arterial Blood				Urine										Respiration							
		$BHCO_3^-$ (mEq./L.)		pH_a		P_aCO_2		pH		$BHCO_3^-$ (mM/L.)		Na^+ (mEq./L.)		K^+ (mEq./L.)		Cl^- (mEq./L.)		$\dot{V}_e/M^2$		R		$\dot{V}O_2/M^2$		$P_{A_{O_2}}$	
		Control	4 hr.	Control	4 hr.	Control	4 hr.	Control	4 hr.	Control	4 hr.	Control	4 hr.	Control	4 hr.	Control	4 hr.	Control	4 hr.	Control	4 hr.	Control	4 hr.	Control	4 hr.
A. Patients with Chronic Pulmonary Emphysema																									
M. A.	4.2	29.7	27.1	7.30	7.29	63	59	6.79	7.45	8.06	.....	60	105	34	34	64	44	4.13	4.65	.80	.75	118	128	72	73
B. M.	6.3	26.3	22.4	7.32	7.28	53	49	5.66	7.65	0.06	15.55	85	168	29	82	104	53	5.98	7.28	.74	.76	166	199	82	89
H. R.	3.2	33.2	32.5	7.31	7.31	70	69	....	....	.....	.....	...	...	...	...	...	...	3.86	4.03	.75	.75	95	100	61	62
	3.5	34.4	31.6	7.28	7.23	76	79	6.23	7.37	14.99	32.73	138	325	60	94	161	145	4.10	3.43	.79	.81	96	82	57	54
	6.5	34.6	32.5	7.35	7.31	66	68	6.76	7.26	10.2	91.2	91	405	74	158	188	306	3.84	4.05	.74	.74	96	101	64	61
J. T.	4.2	34.2	32.3	7.27	7.25	79	79	5.96	7.26	1.0	110.4	13	143	21	79	19	36	7.62	8.21	.87	.87	199	216	60	60
J. W.	2.2	43.8	34.8	7.29	7.23	94	86	6.40	7.47	5.0	50.9	96	449	42	110	113	147	4.57	4.29	.83	.82	130	122	41	49
	4.4	36.2	30.1	7.26	7.21	82	79	5.56	7.38	0.07	76.2	49	140	30	63	80	61	3.95	3.87	.83	.83	117	115	54	54
B. Patients without Lung, Heart or Kidney Disease (Patient A. F. not studied.)																									
C. B.	3.8	21.2	19.1	7.38	7.31	37	39	6.37	7.48	2.4	20.3	197	332	103	144	...	125	4.20	5.27	.75	.83	123	138	102	103
H. B.	4.2	26.0	22.0	7.40	7.37	44	40	6.60	7.48	5.6	78.5	76	348	30	77	80	175	4.52	5.04	.84	.83	107	120	99	103
	4.8	24.7	20.8	7.42	7.39	39	36	6.79	7.51	12.9	104.9	65	249	31	52	50	67	5.25	4.67	.75	.75	101	96	97	101
J. N.	4.0	25.0	21.9	7.40	7.38	42	38	6.31	7.50	4.4	144.0	85	247	74	113	109	62	3.74	4.30	.78	.77	111	119	98	103
L. S.	3.7	23.4	21.8	7.43	7.33	37	44	6.24	7.37	.....	.....	31	124	18	45	36	48	3.33	3.31	.69	.70	96	92	97	89

* Symbols used in tables:

$\dot{V}_e/M^2$ = minute volume of expired gas, i.e., ventilation, in L./min., BTPS
f = respiratory rate in breaths per minute
V_T = tidal volume, in ml. BTPS
$\dot{V}CO_2/M^2$ = CO_2 output, in ml./min./M^2 body surface, STPD
$\dot{V}O_2/M^2$ = O_2 consumption, in ml./min./M^2 body surface, STPD
R = the CO_2:O_2 exchange ratio or respiratory quotient
Sa = per cent oxygen saturation of arterial blood
pHa = pH of arterial blood
$PaCO_2$ = arterial pCO_2, in mm. Hg
$P_{A_{O_2}}$ = alveolar pO_2, in mm. Hg
rO_2 = inspired air oxygen content

plasma bicarbonate fell and there was no change in sodium and potassium plasma levels. The level of alveolar pO_2 rose moderately when arterial pCO_2 fell. These changes reflected improved alveolar ventilation and were accompanied by either a moderate degree of hyperventilation or an increase in the depth of breathing and a slight slowing of rate of respiration, in the absence of hyperventilation.

Effect of Prolonged Administration of Diamox Every Six Hours. Patients with pulmonary emphysema and elevated arterial pCO_2: The effect of ingestion of 2.2 to 6.3 mg./kg. of diamox every six hours was studied during eight different courses of therapy in this group of five patients. A course of therapy lasted from three to twelve weeks except in patient B. M., in whom the drug was discontinued at the end of twelve days because of an exacerbation of chronic bronchiectasis.

These studies were not designed to determine when inhibition of acidification of the urine ceased but it was noted that, with few exceptions, alkalinization of the urine no longer occurred after a few days of continued administration of the drug. During the eighth week of therapy patient J. W. excreted an alkaline urine in the interval between the second and fourth hours without an associated sodium, potassium, bicarbonate or chloride diuresis. In this interval the arterial pCO_2 fell from 91 to 82 mm. Hg and plasma bicarbonate level from 33.9 to 32.2 mEq./L. In studies extending over nearly nine weeks in patient J. T. the reaction of the urine consistently changed from acid to alkaline during the four hours following each morning dose of diamox. Only following the initial dose was this accompanied by a sodium, potassium and bicarbonate diuresis and a fall in the level of plasma bicarbonate. (Table II.)

The maximum reduction in the level of plasma bicarbonate following ingestion of the drug occurred fairly promptly and thereafter remained relatively unchanged. The earliest noted occurred within four hours (J. W., Table II). In some instances it was evident within the first two days, in others between the second and seventh days. The sustained reductions in the level of plasma bicarbonate were either highly significant ($P < 0.01$) or significant ($P < 0.05$) in all patients. (Table III.)

In all five patients the plasma chloride level usually rose to replace the fall in plasma bicarbonate. There sometimes was a transient fall in the level of plasma potassium during the first few days of diamox ingestion. The plasma sodium level remained unchanged.

In two patients of this group (B. M., M. A.) the level of arterial pCO_2 was stable and fell significantly ($P < 0.05$) or highly significantly ($P < 0.01$) (Table III) simultaneously with the plasma bicarbonate. Only patient B. M. exhibited a significant reduction in arterial pH due to a relative and absolute greater fall in plasma bicarbonate level than in arterial pCO_2.

A sustained rise in the level of alveolar pO_2 occurred in both these patients along with the fall in arterial pCO_2. This was associated with hyperventilation in patient B. M. Patient M. A. did not exhibit hyperventilation or a change in the graphically recorded respiratory pattern. Neither patient exhibited a rise in arterial blood oxygen saturation while on diamox. Only patient M. A. attained a normal arterial blood oxygen saturation level during inhalation of 100 per cent oxygen

In the three remaining patients in this group (J. W., J. T. and H. R.) the level of arterial pCO_2 often fluctuated considerably above and below control levels from day to day and frequently during the course of the morning and early afternoon of the same day in the absence of change in clinical state and respiratory gas exchange ratio, R.Q. Their mean level of arterial pCO_2 and pH was not significantly altered as compared with the control periods. (Table III.)

Two of these latter patients, J. T. and J. W., offered an opportunity to evaluate the diuretic effect of diamox. J. T., whose congestive heart failure was poorly controlled with digitalis, ammonium chloride, mercuhydrin, aminophylline and a low-salt diet did not exhibit weight loss during seven and one-half weeks of diamox administered every six hours. During the first twenty-three days each dose was 2.3 mg./kg. and from the twenty-fourth day onward each dose was 3.6 mg./kg. He exhibited a biochemical response to the drug as manifested by a prompt fall in the level of plasma bicarbonate from 36.4 to 30.1 mEq./L. which was sustained, with minor fluctuations, throughout the period of administration of the drug. Plasma bicarbonate level had already risen forty-eight hours after discontinuance of diamox and was at the control period level when measured a week later. A gain in weight did not accompany the retention of bicarbonate.

Approximately one month later, when his

plasma bicarbonate level was slightly lower and arterial pCO_2 higher than previously, diamox was given in a larger dose, 4.2 mg./kg. every six hours. He was still edematous and his weight stable at 122 pounds. There was a loss of 2 pounds during the first day and of 8 pounds during the second and third weeks. It remained at this level with minor fluctuations during the next month. The patient exhibited approximately the same sustained fall in plasma bicarbonate during this period of study as he did during the first period when there was no weight loss. Upon discontinuance of the drug, plasma bicarbonate returned to its control level within four days. It seems reasonable to ascribe the sustained loss of weight to diamox for the following reasons: the reaction of the urine became alkaline within two to four hours whenever the effect of a single dose was studied, and during the first week following discontinuance of the drug there was a steady gain in weight from 114 to 119 pounds.

TABLE III

STATISTICAL EVALUATION OF CHANGES IN THE ACID-BASE BALANCE DURING LONG-TERM ADMINISTRATION OF DIAMOX

Patient	Dose (mg./kg.)	Days on Diamox	Hours after Dose	Period	No. of Observations	Arterial pCO_2 (mm. Hg)	Plasma $BHCO_3^-$ (mEq./L.)	Arterial pH
A. Patients with Chronic Pulmonary Emphysema								
M. A.	4.2 × 4	58	4‡	Control	6	60 ±3	30.2 ±1.1	7.33 ±.02
				Diamox	5	50* ±2	23.5* ±1.7	7.30 ±.03
B. M.	6.3 × 4	12	4	Control	3	51 ±2	25.5 ±0.8	7.33 ±.02
				Diamox	2	45† ±1	18.0* ±0.4	7.23† ±.00
H. R.	3.3 × 4	84	4‡	Control	7	74 ±9	33.0 ±1.6	7.28 ±.06
				Diamox	4	69 ±7	26.8* ±1.5	7.22 ±.04
J. T.	4.2 × 4	60	4§‡	Control	7	71 ±8	35.7 ±1.3	7.33 ±.06
				Diamox	9	67 ±5	30.2* ±0.7	7.29 ±.04
J. W.	4.4 × 4	80	4§‡	Control	6	87 ±7	39.3 ±2.6	7.28 ±.03
				Diamox	3	77 ±5	31.4† ±1.7	7.24 ±.03
B. Patients without Heart, Lung or Kidney Disease								
C. B.	3.8 × 4	20	4	Control	4	39 ±3	23.1 ±1.5	7.40 ±.02
				Diamox	3	25* ±1	13.2* ±0.1	7.35 ±.02
H. B.	4.2 × 4	28	4‡	Control	2	46 ±2	26.7 ±1.0	7.40 ±.00
				Diamox	3	33* ±1	17.4* ±0.1	7.35* ±.01
A. F.	3.7 × 4	13	4	Control	3	40 ±5	23.7 ±3.0	7.39 ±.03
				Diamox	2	33 ±0	14.7† ±1.1	7.27† ±.03
J. N.	4.0 × 4	28	4	Control	3	42 ±2	25.6 ±1.1	7.41 ±.04
				Diamox	3	34† ±3	17.6* ±0.6	7.34 ±.02
L. S.	3.7 × 4	18	4	Control	2	41 ±6	25.0 ±2.2	7.42 ±.02
				Diamox	2	37 ±5	17.0† ±0.7	7.30 ±.04

Changes of comparable significance in the level of arterial pCO_2, pH and plasma bicarbonate were noted two to three (§) and six (‡) hours after the last dose of diamox.

* $p = <0.01$.

† $p = <0.05$.

The other patient, J. W., managed to remain edema-free by marked limitation of activity and

a low-salt diet. He experienced a 2- to 4-pound weight loss ascribable to diamox during two of three different periods of study. In each study he experienced a prompt 6 to 9 mEq./L. fall in the level of plasma bicarbonate. In the dose range employed (2.2 to 4.4 mEq./L.) there was no relationship between the size of the dose and the absolute fall in plasma bicarbonate level or extent of diuresis.

The immediate response to two individual doses of diamox administered to patient J. W. a week apart resulted in a total fall of 15 mEq./L. plasma bicarbonate, 11 mm. Hg arterial pCO_2 and 0.11 pH units. (Table II.) Within four hours after the first diamox dose of 2.2 mg./kg. there was a 9.0 mEq./L. fall in plasma bicarbonate and an 8 mm. Hg decrease in arterial pCO_2 and a 0.06 decrease in the level of arterial pH. The drug was continued in the same dose every six hours during the following three and one-half days. We do not know whether further change in the acid-base balance of the blood occurred during this interval. Following a diamox-free interval of three and one-half days, during which time the plasma bicarbonate and arterial pCO_2 returned somewhat to their previous levels and the reaction of the urine became acid, the ingestion of a single dose of 4.4 mg./kg. of diamox was followed within four hours by an additional fall of 6.1 mEq./L. plasma bicarbonate, of 3 mm. Hg arterial pCO_2 and of 0.05 pH units. (Table II.) In all, the intermittent administration of the drug resulted in a net fall of 13.7 mEq./L. of plasma bicarbonate (43.8 to 30.1), 15 mm. Hg arterial pCO_2 (94 to 79) and 0.08 pH units (7.29 to 7.21). This was associated with only a 4-pound weight loss.

TABLE IV

AN EXAMPLE OF HYPERVENTILATION DURING LONG-TERM ADMINISTRATION OF DIAMOX (PATIENT C. B.) *

Day of Study	$\dot{V}_E$ per m^2	f	V_T	$\dot{V}O_2$ per m^2	R	VR_{B,pCO_2} †	$P_{A_{O_2}}$	S_a	pH_a	P_aCO_2	Plasma $BHCO_3^-$ (mEq./L.)	Plasma Cl^- (mEq./L.)	Urine pH
Control													
	4.20	13.2	591	123	.75	0.86	102	95	7.38	37	21.2	103.7	6.37
Diamox (3.8 mg./kg. every 6 hr) ‡													
0	5.27	13.3	739	138	.83	2.99	103	95	7.31	39	19.1	106.0	7.48
7	6.21	18.5	619	117	.83	−0.90	118	96	7.33	26	13.2	107.8	7.01
13	6.79	20.8	602	117	.83	−1.62	119	94	7.35	25	13.3	112.2	6.92
20	7.24	20.1	654	120	.92	−2.10	122	98	7.36	24	13.1	112.2	7.01
Post-diamox													
6	5.08	21.7	428	117	.77	1.54	98	97	7.40	41	24.7	100.4	6.93
12	4.31	18.9	417	116	.70	1.70	94	97	7.39	41	23.9	98.1	6.79

* A similar response was exhibited by patients J. N. and L. S., who, like C. B., did not have heart, lung or kidney disease and B. M., who had chronic bronchiectasis and pulmonary emphysema.

† Alveolar ventilation ratio according to Gray.[28]

‡ Observations carried out 4 hours after a morning dose of diamox.

Patients without lung, heart or kidney disease: All of the patients exhibited a significant or highly significant fall in plasma bicarbonate and, in three instances, also of arterial pCO_2. (Table III.) The level of arterial pCO_2 was stable when measured a few times during a four-hour period following a dose of diamox, once the maximum effects of the drug were attained. The decrease in the level of plasma bicarbonate was relatively greater than that of arterial pCO_2 and in two patients (H. B. and A. F.), it was sufficient

to cause a significant or highly significant reduction in the level of arterial pH. (Table III.) The level of alveolar pO_2 rose in all five patients. In three (C. B., J. N. and L. S.,) (Table IV) this was accomplished by hyperventilation characterized by a greater increase in depth than in rate of breathing. The remaining two patients (H. B. and A. F.,) (Table V) did not exhibit hyperventilation but rather an increase in depth and a slight decrease in rate of breathing. All patients in this group exhibited a normal level of arterial blood oxygen saturation which did not increase when the alveolar pO_2 rose while on diamox.

Acidification of the urine was generally inhibited only during the first few days of drug administration. This was accompanied by a diuresis of sodium, potassium and bicarbonate ions.

Effect of Prolonged Administration of Diamox on the Response of Patients with Chronic Pulmonary Emphysema and Respiratory Acidosis to Inhalation of 100 Per Cent Oxygen. Table VI summarizes nine studies in three of the five patients with chronic pulmonary emphysema during inhalation of oxygen* for forty-four to ninety minutes in the control and diamox periods. The change in minute volume of respiration during oxygen inhalation is expressed as per cent of the average of a seven-minute period of room air breathing preceding oxygen inhalation. In nearly all instances average minute volume of respiration decreased while breathing oxygen. Ingestion of diamox did not influence the response. Decrease in minute volume of respiration was associated in four instances with a relatively greater decrease in tidal volume than rate; in two instances these decreased to the same relative degree and in one, rate decreased more than depth. Tidal volume increased in two studies in

TABLE V

PATIENT H. B.—AN EXAMPLE OF A FALL IN $PaCO_2$ WITHOUT HYPERVENTILATION DURING LONG-TERM ADMINISTRATION OF DIAMOX*

Day of Study	$\dot{V}_E$ per m^2	f	V_T	$\dot{V}O_2$ per m^2	R	VR_{H,pCO_2}†	$P_{A_{O_2}}$	S_a	pH_a	P_aCO_2	Plasma $BHCO_3^-$ mEq./L.	Plasma Cl^- mEq./L.	Urine pH
Control													
	4.09	17.6	409	103	.83	....	...	..	....	..	.....	.....	....
	4.52	17.0	467	107	.84	2.29	99	96	7.40	44	26.0	103.5	6.60
Diamox (4.2 mg./kg. every 6 hours)‡													
0	5.04	18.8	472	120	.83	1.87	103	96	7.37	40	22.0	105.0	7.48
5	5.03	15.1	574	120	.85	0.74	110	95	7.35	34	18.2	113.0	7.10
12	5.34	14.8	624	127	.85	0.97	111	95	7.34	34	17.2	111.0	7.06
25	5.19	16.2	551	123	.85	0.21	111	97	7.35	32	16.9	111.6	6.80
Post-diamox													
7	4.16	17.1	418	106	.85	3.07	96	94	7.40	47	27.4	.....	6.51

* Note that the patient exhibited a moderate increase in tidal volume (V_T) with respiratory rate generally remaining the same or slightly slower during the diamox period. A similar response was exhibited by patient A. F., who, like H. B., did not have heart, lung or kidney disease, and patient M. A., who suffered from chronic pulmonary emphysema.

† Alveolar ventilation ratio according to Gray.[28]

‡ Observations carried out four hours after a morning dose of diamox.

* The composition of the gas delivered from commercial tanks varied between 98.95 and 99.16 per cent oxygen and 1.05 to 0.84 per cent nitrogen.

patient H. R. along with a decrease in respiratory rate during the diamox period. Rate of respiration and tidal volume generally varied in opposite directions. In no instance did rate of respiration exceed that while on room air. Periodic respirations characterized by fluctuations in tidal volume and rate of respiration were common. Only patient J. W. exhibited apneic periods, which lasted fifteen to twenty-five seconds. These occurred during one of each of the two studies in the control (April 6, 1953) and in the diamox (July 13, 1953) periods.

There was no over-all consistent relationship between the degree of respiratory depression exhibited by these patients during periods of oxygen inhalation and any of the following: the initial level of plasma bicarbonate and the extent to which it fell under influence of diamox or rose during oxygen inhalation, the initial level of arterial pCO_2 and pH, or the level to which arterial blood oxygen saturation rose. (Table VI.) The level of plasma bicarbonate rose 1.4 to 3.3 mEq./L. in three of five studies on oxygen during control periods and 3.0 and 3.4 mEq./L. in two of six studies during diamox periods. (Table VI.) No patient in whom more than one study was carried out during either control or diamox periods exhibited a compensatory rise in plasma bicarbonate more than once in either period.

Arterial blood oxygen saturation varied between 57 and 80 per cent when breathing room air. It rose to normal in only one patient, M. A., and remained unchanged or increased to between 71 and 92 per cent in the other two patients. It seems reasonable to expect that the level of arterial blood oxygen saturation would stabilize after many minutes of oxygen inhalation in spite of periodic or depressed respirations, whereas the arterial pCO_2 level would vary considerably. The arterial pCO_2 during oxygen inhalation periods listed in Table VI reflects only the level during the intervals of blood withdrawal. This limitation no doubt also applies to arterial pH but to a varying degree depending upon accompanying changes, if any, in plasma bicarbonate level. The acidosis was more intense during inhalation of oxygen in those instances in which fall in plasma bicarbonate during the diamox period was unaccompanied by a significant fall in the level of arterial pCO_2. None of the patients manifested mental or neurologic changes during periods of oxygen inhalation even though there were instances of a considerable rise in the level of arterial pCO_2 and intense acidosis.

DISCUSSION

Immediate Effects of a Single Dose of Diamox in Patients with Chronic Pulmonary Emphysema and in Patients without Lung, Heart and Kidney Disease. The immediate alterations in urinary electrolyte excretion following an oral dose of diamox have been described in detail.[4,11,22,23] The onset of diuresis of sodium, potassium, bicarbonate and water may be noted within about an hour, is apt to reach its peak at approximately ninety minutes, may be complete by four to five hours and may be over in eight hours.[22] The present studies were designed to detect correlated changes in respiration, arterial blood acid-base balance, plasma electrolyte levels and urinary electrolyte excretion during the four-hour interval when the drug exerts most of its effects.

Our patients exhibited considerable variation in the fall of plasma bicarbonate level in response to a single dose of diamox. (Table II.) The responses of patient J. W. suggest that it varies with the initial plasma bicarbonate level but the data on all the patients do not bear out this relationship, nor do the initial levels of arterial pCO_2, oxygen saturation or of pH seem to be closely related. With intravenous administration of diamox in dogs, bicarbonate diuresis is directly proportional to the initial plasma bicarbonate concentration.[24] The response of our patients to oral administration of the drug does not reflect this nor does the intensity of the diuresis vary with the absolute decrease in the level of plasma bicarbonate. (Table II.) Our studies and those of Schwartz et al. are obviously not strictly comparable because of the differences in species studied and because the dietary intake of our patients was not rigidly controlled.

The urine of all of our patients became alkaline between the first and third hours and this was associated with a sodium, potassium and bicarbonate diuresis. Others have demonstrated that in addition to these alterations in urinary electrolyte excretion there is a decrease in titratable acidity and in ammonium ion excretion,[11,23] and a slight[11] or no increase in urinary phosphate.[23] Chloride ion excretion generally remains unchanged.[11] In some instances it rises.[23] Excretion of nitrogen and organic acids remains unchanged.[23]

Although all patients exhibited some fall in the level of plasma bicarbonate, varying from

TABLE VI

STUDIES ON THE RESPIRATORY* AND ACID-BASE BALANCE ADJUSTMENTS TO OXYGEN INHALATION IN PATIENTS WITH CHRONIC PULMONARY EMPHYSEMA DURING CONTROL AND DIAMOX PERIODS

Patient	M. A.				H. R.						J. W.							
Period	Control		Diamox		Control		Diamox				Control				Diamox			
rO_2	Rm Air	100% O_2	Rm Air	100% O_2	Rm Air	100% O_2	Rm Air	100% O_2	Rm Air	100% O_2	Rm Air	100% O_2	Rm Air	100% O_2	Rm Air	100% O_2	Rm Air	100% O_2
Dose (mg./kg.)			4.2				3.3		3.5						2.2		4.4	
Date	6/17/54		4/23/54		5/5/54		7/15/53		4/27/54		4/2/53		4/6/53		5/8/53		7/13/53	
Time on 100% O_2*	58′		58′		45′		45′(67′)		45′		65′(74′)		65′		65′		65′(90′)	
$\dot{V}_E$	7.35	−14.5	7.68	−7.9	6.98	−12.9	8.54	−19.0	6.74	−0.4	7.04	−44.1	5.73	−31.3	6.46	−46.2	6.24	−42.6
V_T	417	−12.3	423	−7.1	342	−6.7	339	+3.4	316	+12.8	371	−27.9	356	−26.0	366	−25.5	365	−18.5
f	17.6	−2.5	18.1	−0.7	20.4	−6.3	25.2	−21.6	21.8	−11.8	19.0	−21.6	16.1	−6.6	17.6	−25.0	17.1	−28.4
S_a	80.4	98.6	77.4	96.7	65.9	83.7	72.2	92.3	62.9	83.4	62.8	84.0	56.8	74.0	64.0	83.7	68.2	71.3
pH_a	7.34	7.31	7.31	7.29	7.30	7.18	7.24	7.19	7.23	7.17	7.28	7.18	7.27	7.09	7.20	7.05	7.21	7.05
P_aCO_2	61	69	51	55	64	88	69	78	76	88	81	110	87	133	83	127	88	127
Plasma $BHCO_3$ (mEq./L.)	31.7	33.8	25.1	25.8	30.5	31.9	28.1	28.3	30.7	31.2	35.8	39.1	38.2	38.2	31.0	34.1	34.1	34.1
Plasma Cl^-(mEq./L.)	95.7	95.0	103.9	107.0	95.7	93.6	102.8	102.1	101.5	102.5	95.5	95.8	92.2	94.5	....	.....	103.1	101.9

* The respiratory data during 100 per cent oxygen inhalation in the control and diamox periods are based upon the average values of intervals of the same number of minutes. They are expressed as per cent increase (+) or decrease (−) as compared with a preceding seven minute room air period. The minutes enclosed in parentheses indicate instances where oxygen inhalation was continued for longer periods of time. There were no significant changes in the average values over these more prolonged periods. Arterial blood samples were collected during the second to fifth minutes of the last seven minutes of oxygen inhalation. The graphic respiratory tracings were measured minute by minute. Only patient J. W. exhibited Cheyne-Stokes breathing while inhaling oxygen. He exhibited apneic intervals of 15 to 25 seconds in the first fifteen minutes of oxygen inhalation on April 6, 1953 and in the seventh, fifty-fourth and fifty-eighth minutes on May 8, 1953 and at no time during blood collection.

0.7 to 9.0 mEq./L. (generally 2 to 4 mEq./L.), within four hours of ingestion of a dose of diamox, the level of arterial pCO_2 either remained essentially unchanged or fell 4 to 8 mm. Hg. In one patient, L. S., it was 7 mm. Hg higher. Arterial pH either remained unchanged or fell 0.04 to 0.10 units, in these instances generally reflecting the relatively greater fall in plasma bicarbonate.

In those instances in which plasma bicarbonate and arterial pCO_2 fell simultaneously within four hours after a single dose of diamox, a moderate rise in alveolar pO_2 and minute volume of alveolar ventilation occurred. This was associated with one of two different alterations in the pattern of respiration. Some patients exhibited a moderate degree of hyperventilation (an increase in ventilation in excess of metabolic needs) presumably stimulated by the fall in plasma bicarbonate. In others, more effective alveolar ventilation appeared to be accomplished by a moderate increase in depth and slight slowing in rate of respiration in the absence of compensatory hyperventilation. Review of Roughton's studies on the response of healthy adults to a single dose of sulfanilamide which as pointed out previously is a less potent carbonic anhydrase inhibitor than diamox, indicates that some of them likely responded in this latter manner.[2]

Effect of Prolonged Administration of Diamox Every Six Hours to Patients with Pulmonary Emphysema and Elevated Arterial pCO_2 and to Patients without Lung, Heart and Kidney Disease. The return of the urinary electrolyte excretion pattern to control period levels within two to three days and its persistence with continued administration of diamox a few times a day has been well documented.[11,22,23] Although we did not carry out metabolic balance studies, some data confirming the transitory nature of the alterations in urinary electrolyte excretion were obtained. A few-fold increase in the dose of diamox does not alter this situation. Unresponsiveness to the drug may, however, appear after the initial dose.[23] This was evident with regard to decrease in the level of plasma bicarbonate in patient J. W., who exhibited as great a fall in plasma bicarbonate following the initial dose of diamox in each of two different courses of therapy as he did during days to weeks of continuous ingestion of the drug. His urine was not examined at sufficiently frequent intervals to note whether the renal effects of the drug were short-lived.

Friedberg and his co-workers[22] and also Belsky[25] reported continued effectiveness of a single daily dose of 0.25 to 0.5 gm. of diamox based on loss of body weight in the treatment of patients suffering from congestive heart failure in the outpatient department. In contrast, in carefully controlled metabolic studies in hospitalized patients suffering from congestive heart failure Leaf[23] and Relman[26] observed fairly prompt refractoriness to the drug when given once daily or every other day.

Another exception to the usual transient response to the drug is the observation that urinary acidification may continue to be inhibited for eight and one-half weeks (4.2 mg./Kg. every six hours, patient J. T.) and for as long as four weeks of a twenty-week course of a daily dose (3.5 mg./kg., patient H. R.). Only during the first few days of these two studies was alkalinization of the urine associated with sodium, potassium and bicarbonate diuresis. Leaf also noted inhibition of urinary acidification without sodium diuresis in three patients with congestive heart failure.[23] In two of these patients there was an equivocal or slight increase in urinary potassium, associated with water diuresis in only one instance. A definite potassium diuresis occurred in two different studies in the third patient.

It is generally agreed that a reduction in plasma bicarbonate level accompanies the urinary electrolyte diuresis.[27] By the second to the seventh day of continued administration of the drug, peak reduction in the level of plasma bicarbonate of about 5 to 10 mEq./L. below the control level occurs.[11] Plasma chloride often rises to approximately the same degree as the bicarbonate level falls, resulting in hyperchloremic acidosis. Although the diuresis is transient the reduced level of plasma bicarbonate persists.

There is, however, conflict in the evidence concerning the adjustment of the acid-base balance of the blood to long-term ingestion of the drug. Leaf observed sustained hyperchloremic acidosis for as long as eleven days in normal subjects and in patients with pulmonary emphysema and respiratory acidosis.[23] Nadell noted in similar groups of patients a return of the acid-base balance of the blood to normal associated with a fall in the level of arterial pCO_2 after one to two weeks of treatment.[11] The fall in arterial pCO_2 was logically attributed to compensatory hyperventilation stimulated

by the acidosis which resulted from the diamox-induced fall in plasma bicarbonate. This led to the conclusion that diamox brings about more effective dissipation of carbon dioxide in the lungs.[11] It also indicates delayed onset of an altered sensitivity of the respiratory regulatory mechanism to a decrease in the level of plasma bicarbonate.

However, measurements of minute volume of respiration, oxygen consumption and respiratory gas exchange ratio (R.Q.), which appear essential to establish whether the delayed fall in the level of arterial pCO_2 actually reflects metabolically induced conpensatory hyperventilation, were not carried out. A transitory fall of a few millimeters Hg in the level of arterial pCO_2 and rise in arterial pH accompanied by little or no fall in plasma bicarbonate may result from moderate hyperventilation induced by the discomforts of an experimental procedure. The influence of such stimuli would no doubt be distinguished by an inconsistency in the results of frequent respiratory measurements along with measurements of arterial blood pH, pCO_2, plasma bicarbonate levels and of arterial blood pressure and pulse rate. Therefore, in our studies such observations were carried out, as described under *Methods*.

In no instance did we observe a lag of a week or two in the fall of arterial pCO_2 behind that of plasma bicarbonate, nor a rise in the mean level of arterial pH to normal in the chronically acidotic patients, nor a return to the control pH values in the patients without lung, heart and kidney disease. However, although the mean arterial pH was lower during the diamox period in all patients, it was significantly reduced in only one of the patients with chronic pulmonary emphysema and in three of the patients without lung, heart and kidney disease. The prompt partial respiratory compensation for the diamox-induced metabolic acidotic component (decrease in plasma bicarbonate) noted by us, rather than a delayed complete compensation, is to be expected according to Gray's studies on the integrated regulation of pulmonary ventilation.[28] Gray points out that "since the factor which initiates and maintains the ventilatory adjustment is the pH change itself, the compensation cannot be sufficient to restore the original pH, for this would eliminate the respiratory stimulus which is driving the compensatory mechanism" (ref. 28, p. 54).

It is known that in normal individuals an acute fall in arterial pH resulting from plasma bicarbonate depletion is a feeble respiratory stimulus as compared to a similar fall in the level of arterial pH resulting from sudden elevation of arterial pCO_2.[28] Patients suffering from pulmonary emphysema associated with carbon dioxide retention exhibit considerably less respiratory stimulation than normal individuals from an acute elevation in the level of arterial pCO_2 upon inhalation of mixtures of carbon dioxide and high oxygen.[29–31] It might therefore be expected that such individuals would be even more insensitive to a fall in arterial pH resulting from a decrease in the level of plasma bicarbonate.

Donald and Christie,[30] and Tenney[31] reported a diminished ventilatory response to carbon dioxide in patients suffering from pulmonary emphysema, to a degree which is proportional to the level of carbon dioxide retention in their blood. Tenney also noted that increased responsiveness to this stimulus developed in these patients one to two days after their blood carbon dioxide content fell as a result of the ingestion of 10 mg./kg./24 hours of diamox.[31] This lag in the onset of increased ventilatory response was ascribed to a probable readjustment of the sensitivity of the respiratory center from adaptation to an elevated blood pCO_2 level.

Tenney suggested that this mechanism might account for the delay of one to two weeks in the fall of arterial pCO_2 in patients with chronic pulmonary emphysema and respiratory acidosis treated with diamox by Nadell.[11] However, since it is known that the respiratory center of normal individuals is exquisitely sensitive to minor alterations in arterial pH and pCO_2 it is difficult to involve the same reasoning to explain the similar lag noted in normal subjects by Nadell.

Although Fishman et al. also noted a return of arterial pCO_2 and plasma bicarbonate to normal levels in patients with chronic pulmonary emphysema and carbon dioxide retention treated with diamox, these patients did not then, contrary to Tenney's findings, exhibit an increased responsiveness to inspired CO_2.[32] The response of these patients was not influenced by the level of arterial hypoxemia, pH or red blood cell mass and reduced ventilatory capacity was excluded as a cause for failure of ventilation to increase. It was concluded that such patients suffer from permanent injury to the respiratory center. These studies did not, how-

ever, account for the manner in which the level of arterial pCO_2 fell. Our studies, as has previously been discussed, indicate that this may come about by different patterns of ventilatory adjustment which have a common net effect. This was noted in both groups of patients studied.

It is of interest to analyze the respiratory adjustments of our patients to carbonic anhydrase inhibition according to Gray's concepts of the integrated chemical regulation of pulmonary ventilation.[28] Gray derived a multiple linear equation* which describes quantitatively the partial effects of changes in arterial blood H^+ concentration, pCO_2 and pO_2 on ventilation. It involves the assumption of an equality in the levels of arterial and alveolar pCO_2 and pO_2. It is known that such relationships do not exist in the presence of pulmonary emphysema. The formula may therefore be used with confidence only in those of our patients without lung, heart and kidney disease. Variations in the level of arterial pO_2 above 80 mm. Hg have no effect on respiration in this formula. Although we did not measure arterial pO_2 directly, the values derived by interpolation from the oxygen dissociation curve fell above the 80 mm. Hg level in all our patients without lung, heart and kidney disease. The changes in the level of arterial pO_2 may therefore be disregarded in these patients.

When Gray's formula is applied in this manner to instances of metabolic acidosis, it can be seen that an increase in H^+ concentration due to plasma bicarbonate depletion stimulates respiration. This leads to a fall in arterial pCO_2. The fall in the level of arterial pCO_2 depresses respiration. The net effect of these two opposing respiratory stimuli is an increase in ventilation in excess of metabolic requirements, reflected by a greater VR_{H,pCO_2} ratio as compared with the pre-acidotic state.

Under the influence of prolonged administration of diamox, the alveolar ventilation ratio, VR_{H,pCO_2}, of our patients falls below that of the control period (Tables IV, V). This indicates that the inhibitory effect on ventilation of the decreases in the mean level of arterial pCO_2 exceeded the stimulatory effect of the relatively minor decreases in the mean levels of arterial pH. Had ventilation been regulated in these patients during the diamox periods solely by these chemical stimuli, according to Gray's views, it would have ceased or been depressed as compared with the control periods.[28] The fact that the measured volumes of alveolar ventilation increased in all patients in whom the mean level of arterial pCO_2 fell significantly indicates, according to Gray's concepts, that some other respiratory stimulus must have been operating. Whether this is due to direct or reflex stimulation of the respiratory center by carbonic anhydrase inhibition is not evident.

The fact that in all instances the changes in respiration noted by us no longer occurred when the level of arterial pCO_2 and plasma bicarbonate returned to control levels following cessation of diamox therapy makes it seem likely that they were causally related to the effects of the drug.

Three of the five patients (J. W., J. T., H. R.) with advanced pulmonary emphysema and respiratory acidosis exhibited considerable fluctuations in the level of arterial pCO_2 from day to day and during the morning and early noon of the same day in the absence of change in clinical manifestations or in minute ventilation and respiratory gas exchange ratio (R.Q.). (Table III.) The evidence indicated that spontaneous variations in effectiveness of alveolar ventilation were occurring without adequate explanation. These findings serve to emphasize the limitations of ascribing a decrease in the level of arterial pCO_2 to diamox in such patients and the importance of statistical evaluation of their significance.

Studies on the Effect of Prolonged Administration of Diamox on the Response of Patients with Chronic Pulmonary Emphysema and Respiratory Acidosis to the Inhalation of 100 Per Cent Oxygen. It is currently believed that the respiratory drive of patients suffering from pulmonary emphysema associated with anoxemia and carbon dioxide retention is maintained by anoxic reflex stimuli arising in the carotid and aortic bodies. Acute relief of anoxemia by oxygen inhalation causes a suppression of the respiratory drive. Minute volume of respiration therefore decreases and as a result the level of arterial pCO_2 rises. Mental and neurologic symptoms develop in

* In this equation $VR_{H,pCO_2,pO_2} = 0.22H + 0.262\ pCO_2 - 18 + 2.118 \times 10^{-8}\ (104 - pO_2)^{4.9}$. VR refers to alveolar ventilation ratio. This is the alveolar ventilation expressed as a multiple of the resting ventilation. The subscript symbol, H, represents the H ion concentration of arterial blood expressed in billionths of moles per liter and similarly pCO_2 and pO_2 refer to their tensions in arterial blood.[28]

about 10 per cent of these patients during oxygen inhalation, for reasons which are not fully understood.[13] There is disagreement concerning the biochemical changes in the blood which predispose to these potentially serious complications. Some have indicated that the primary factor is a sharp fall in arterial pH due to failure of plasma bicarbonate level to rise along with the increase in arterial pCO_2.[12,33] Comroe has emphasized that the elevated arterial pCO_2 level is the determining factor.[13] It was believed that some data which bear upon both these concepts might be obtained by comparison of the respiratory, biochemical and clinical responses to inhalation of 100 per cent oxygen, before and during diamox administration, in the patients with pulmonary emphysema who exhibited only a significant fall in plasma bicarbonate and in the patients who, in addition, exhibited a fall in arterial pCO_2 during the diamox period. According to the views of Barach[12] and Richards,[33] a decrease in the level of plasma bicarbonate, unaccompanied by a fall in arterial pCO_2 during the diamox period, might be expected to increase the severity of respiratory depression during inhalation of oxygen and predispose to the development of mental symptoms and neurologic disturbances. This would be more likely to occur in those instances in which a compensatory ri e in plasma bicarbonate did not take place during oxygen inhalation. It was a fortunate coincidence that the level of arterial pCO_2 and arterial blood oxygen saturation varied very little in certain groups of studies (Table VI) carried out during the control and diamox periods in patient J. W., which made it possible to evaluate this concept. It is evident that this patient did not exhibit a greater decrease in minute volume of respiration on oxygen following intensification of acidosis due to a fall in plasma bicarbonate level during the diamox period. Similarly, failure of plasma bicarbonate level to rise during oxygen inhalation in the control and diamox periods did not alter the degree of respiratory depression. In no instance did the patient develop mental and neurologic symptoms.

The studies of Comroe et al.[13] suggest a potential beneficial effect of diamox in the prevention of mental symptoms during inhalation of oxygen in patients in whom it brings about a reduction in arterial pCO_2 to less than 50 mm. Hg. They concluded on the basis of studies in sixty-five patients with chronic pulmonary emphysema that mental symptoms occur only in patients with an arterial pCO_2 level of 50 mm. Hg or more, associated with anoxemia, which is relieved by inhalation of oxygen. Unfortunately for the purpose of evaluating the possible beneficial effects of the drug, none of our patients experienced mental symptoms during either the control or diamox periods. It was thought, however, that in keeping with Comroe's view those patients who experienced a significant fall in the level of arterial pCO_2 during diamox therapy might exhibit less respiratory depression during oxygen inhalation. Such studies could be carried out only in one (M. A.) of the two patients who exhibited a significant fall in the level of arterial pCO_2 (from 61 to 51 mm. Hg) and of plasma bicarbonate (from 32 to 25 mEq./L.) during diamox therapy. Arterial blood oxygen unsaturation was also relieved in this patient by oxygen inhalation. (Table VI.) He did not exhibit less respiratory depression during oxygen inhalation in the diamox period than during the control period.

A potential disadvantage resulting from the use of diamox was exhibited by patient J. T. when bronchopneumonia developed complicated by a rise in the level of arterial pCO_2 and a fall in the level of plasma bicarbonate during a course of diamox therapy. In the absence of this complication the patient exhibited a fall in the mean level of plasma bicarbonate from 35.2 to 30.9 mEq./L. associated with statistically insignificant changes in the level of arterial pCO_2 and pH. (Table III.) While suffering from bronchopneumonia plasma bicarbonate level fell an additional 4.9 mEq./L., i.e. to 26 mEq./L., and arterial pCO_2 rose to 100 mm. Hg and arterial pH fell to 7.05. It can be estimated by the graphic method of Davenport[34] that for this rise in the level of arterial pCO_2 arterial pH would have fallen to only 7.20, if one makes the reasonable assumption that in the absence of diamox ingestion mean plasma bicarbonate level would have fallen from 35.2 mEq./L. to only 30.3 mEq./L. during the bronchopneumonia. Even greater intensification of the acidosis would occur should such a patient experience ventilatory depression and carbon dioxide retention during oxygen therapy, which is commonly administered in the presence of bronchopneumonia. It is, of course, likely that partial compensation for the increase in arterial pCO_2 would occur as a result of increased renal bicarbonate

reabsorption stimulated by the rising arterial pCO_2.[35–37]

Another potential disadvantage in the use of diamox, should clinical complications associated with either carbon dioxide retention or plasma bicarbonate depletion, or both, develop is the delay of about three to five days in the rise of plasma bicarbonate to its usual level following discontinuance of the drug.

The marked sensitivity of the respiratory regulatory mechanism of patients with chronic anoxemia to only minor increases in arterial blood oxygen saturation is illustrated by the studies carried out in patient J. W. A rise of only 3 per cent during oxygen inhalation on July 13, 1953, was associated with a 42.6 per cent decrease in minute volume of respiration. (Table VI.) Similarly on April 6, 1953, when he exhibited a comparable degree of anoxemia during oxygen inhalation, minute volume of respiration was 31.3 per cent less than when breathing room air. (Table VI.)

These studies demonstrate that the respiratory depression during oxygen inhalation is not of the same intensity in different patients who exhibit comparable degrees of anoxemia in room air and during oxygen inhalation. Patient H. R., starting from approximately the same level of arterial oxygen saturation, attained 84 per cent saturation on April 27, 1954, and May 5, 1954. However, his average minute volume of respiration was depressed 12.7 per cent on May 5, 1954, and only 0.4 per cent on April 27, 1954. (Table VI.) Similarly, patient J. W. attained the same degree of arterial oxygen saturation (84 per cent) on April 2, 1953, and May 8, 1953, associated with about 45 per cent decrease in respiration. (Table VI.) These observations indicate that in these patients with chronic anoxemia the level of arterial blood oxygen saturation is not the sole stimulus for regulation of the minute volume of respiration. It is possible that the presence of heart failure contributed to the greater respiratory depression in patient J. W. as compared with patient H. R. In this regard, Comroe et al.[13] reported that of nine chronically anoxemic patients who exhibited mental symptoms during oxygen inhalation, six were in congestive heart failure.

SUMMARY

Studies of the immediate and long-term effects of the ingestion of 2.2 to 6.3 mg./kg. diamox, given every six hours, on acid-base balance of the blood, plasma electrolyte levels, urinary electrolyte excretion rates, respiration and metabolic rate were carried out in five patients suffering from chronic lung disease and respiratory acidosis, and in five patients without lung, heart and kidney disease.

Within four hours after the ingestion of a single dose of diamox both groups of patients exhibited a fall in the level of plasma bicarbonate and alkalinization of the urine with a diuresis of sodium, potassium and bicarbonate ions. The alterations in the level of arterial pCO_2 were variable and arterial pH either remained unchanged or fell moderately. The intensity of these changes bore no relationship to the size of the dose of diamox, the initial levels of plasma electrolytes, arterial pH or oxygen saturation.

Alkalinization of the urine and diuresis of sodium, potassium and bicarbonate no longer occurred after the first few days in all but one patient, who suffered from heart failure associated with chronic pulmonary emphysema and cor pulmonale. He exhibited inhibition of acidification of the urine without electrolyte diuresis throughout an eight and one-half week study period.

Prolonged administration of the drug was accompanied in all the patients by a significant fall in the level of plasma bicarbonate. Arterial pCO_2 fell significantly in three and arterial pH in two of the patients without heart, lung or kidney disease. Two of the emphysema patients exhibited a significant decrease in arterial pCO_2 and one an intensification of acidosis. Arterial pH did not rise to a normal level in the emphysema patients, nor to control values in the patients without lung, heart or kidney disease. Arterial pCO_2 often fluctuated considerably, without apparent cause, in the course of a morning and from day to day in control and diamox periods in three of the chronic emphysema patients.

Hyperventilation or an increase in tidal air and a moderate slowing in rate of respiration, while minute volume of respiration remained relatively unchanged, accounted for the instances of sustained decrease in arterial pCO_2, rise in alveolar pO_2 and alveolar ventilation.

The ventilatory adjustments to prolonged administration of diamox appear to involve a stimulus or stimuli other than those included in Gray's multiple chemical factor theory of the regulation of ventilation.

Intensification of acidosis by diamox-induced fall in plasma bicarbonate in the chronic emphysema patients did not alter their degree of respiratory depression during inhalation of 100 per cent oxygen and the response of one such patient was not less depressed when there was a concomitant reduction in the level of arterial pCO_2.

Potential disadvantages to the administration of diamox every six hours in some patients with chronic respiratory acidosis are intensification of the acidosis due to depletion of plasma bicarbonate and a delay of a few days in its return to control levels following discontinuance of the drug.

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Ventilatory Drive in Chronic Pulmonary Emphysema*

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In patients with chronic, diffuse, obstructive pulmonary emphysema, a disease characterized anatomically by narrowing of the bronchioles and loss of pulmonary elasticity,[1] the capacity to increase minute ventilation ($\dot{V}_E$)† is an important compensatory mechanism for disturbed alveolar ventilation-perfusion relationships, which constitute a fundamental physiologic aberration of this disease. The defects in distribution, physiologically equivalent to augmented dead space ventilation and venous admixture, would in the absence of compensatory mechanisms impede the elimination of CO_2 from the blood, thereby damming up CO_2 in the large tissue-fluid reservoir; the retention of CO_2 would, in turn, lead to an increase in alkali reserve mediated by the kidney. The respiratory mechanisms available to counteract the tendency to CO_2 retention include (1) the ability of the respiratory center to augment the ventilatory drive, thereby promoting a larger $\dot{V}_E$ and effective alveolar ventilation ($\dot{V}_A$), and (2) the capacity of the chest bellows to respond to an augmented ventilatory drive.

It has long been known[2–5] that in some patients with chronic pulmonary emphysema there is only a slight increase in $\dot{V}_E$ when CO_2 is added to inspired air. This limited ventilatory response has been ascribed to (1) reduction of the maximum ventilatory capacity, (2) increased buffering capacity of arterial blood and (3) depression of the responsiveness of the respiratory center to the stimulus of an increased partial pressure of CO_2 in arterial blood. The potential role of this last mechanism is suggested by experimental observations which demonstrate that in dogs variations in P_{CO_2}, hydrogen ion concentration and alkali reserve of arterial blood and cerebrospinal fluid influence the responsiveness of the respiratory center to the CO_2 stimulus. The therapeutic implication of these observations prompted Boutourline-Young and Whittenberger[9] to attempt restoration of the sensitivity of the respiratory center to the P_{CO_2} stimulus in two patients with chronic pulmonary emphysema and CO_2 retention. For this purpose they used controlled, mechanically-induced, prolonged hyperventilation in order to effect a reduction in arterial blood P_{CO_2} and alkali reserve.

The present study was planned with the following objectives: (1) to identify physiologically the type of patient with chronic pulmonary emphysema in whom there is a reduced ventilatory drive; (2) to determine the mechanisms responsible for the limited increase in $\dot{V}_E$ during CO_2 breathing in these patients, and (3) to evaluate, in patients with chronic pulmonary emphysema and long standing CO_2 retention, the effect on the regulation of respiration of a reduction in arterial blood P_{CO_2} and alkali reserve achieved by the use of a carbonic anhydrase inhibitor. These three aspects of the present investigation are of considerable importance in the medical management of individual patients with this disease.

Subjects for Study

To facilitate this presentation the patients are classified into three homogeneous groups and a

† Abbreviations are in accordance with the suggestions of the Committee on Standardization of Symbols in Respiratory Physiology. *Fed. Proc.*, 9: 602, 1950.

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fourth miscellaneous group. The first group consists of eleven hospital "normal" subjects free of cardiac or pulmonary disease serving as controls. The second group consists of twelve patients with chronic pulmonary emphysema without CO_2 retention at the time of study and without a medical history suggestive of previous CO_2 retention; these patients will be referred to as patients with emphysema without CO_2 retention. The third group consists of thirteen patients with chronic pulmonary emphysema complicated by CO_2 retention and arterial hypoxemia; these patients will be referred to as patients with emphysema with CO_2 retention. The diagnosis of chronic pulmonary emphysema was established in each patient in accord with criteria previously described.[4] The fourth group consists of six patients with either cardiac disease or pulmonary disease other than chronic pulmonary emphysema and includes two patients (C. S., B. B.) with congestive heart failure, two patients (N. P., G. L.) with secondary polycythemia due to congenital heart disease, one patient (W. W.) with severe primary anemia (6 gm. of hemoglobin per 100 ml. of blood) and one patient (E. H.) with diffuse pulmonary granuloma. Hence five of the six patients had one physiologic abnormality, that is, either polycythemia, chronic hypoxemia, anemia or slowed circulation which might *per se* alter the ventilatory response to inspired carbon dioxide, while the sixth had a chronic pulmonary lesion quite different from emphysema. Pertinent statistics concerning all control subjects and patients are included in Table 1.

The control subjects were studied following recovery from their illness prior to discharge from the hospital. Most of the patients with chronic pulmonary emphysema were ambulatory. Since clinical recognition of an acute upper respiratory infection may be difficult in patients with chronic pulmonary emphysema, particular care was exerted not to study any patient during an overt exacerbation of pulmonary disease. The data in Table 1 were obtained after a period of training and adaptation to the procedures, to the personnel and to the laboratory surroundings; this period of training was required in order to obtain consistent and reproducible ventilatory responses during control and experimental periods. Patients who had been previously studied in the laboratory required little or no training; others required one or more training periods before they could tolerate concentrations of 1 to 5 per cent CO_2 in inspired air without anxiety and with satisfactory evidence of stabilization of the respiration and circulation, such as constancy of ventilation, heart rate, oxygen uptake and respiratory exchange ratio.

All patients were continued on regular treatment schedules. For the emphysema patients without CO_2 retention this was largely confined to inhalations of bronchodilator sprays. The emphysema patients with CO_2 retention were, in addition, usually on low-salt diets and were receiving maintenance doses of digitalis and mercuhydrin® in accord with their clinical needs; seven patients in this group were also treated with diamox,® a carbonic anhydrase inhibitor,* the general trend of the disease in these patients had been documented in this laboratory by repeated ventilatory studies and arterial blood analyses during periods of observation extending up to four years.

METHODS

All patients were studied in the postabsorptive basal state without preliminary sedation. The series of gas mixtures routinely used were 0, 1, 3 and 5 per cent CO_2 in air. Each mixture of CO_2 in air was breathed for twelve to twenty minutes and samples of gas for analysis were collected during the last one and one-half to two minutes of each period. At least twenty minutes of breathing of room air elapsed between runs. This time schedule was based on the demonstration both in normal subjects and in patients with emphysema that (1) ventilation reached a constant level after approximately ten minutes of 5 per cent CO_2 breathing (Fig. 1), (2) arterial blood P_{CO_2}, pH and oxyhemoglobin saturation also reached a plateau at ten minutes and (3) arterial blood P_{CO_2}, pH and oxyhemoglobin saturation had returned to control levels by the twentieth minute of recovery on ambient air. The purpose of the preliminary studies and the experimental plan was to reach and maintain a "steady state" of respiration and circulation[10] and a stable gaseous composition of tissue fluids (particularly with respect to CO_2) so that arterial blood P_{CO_2} and pH might reflect the chemical stimuli at the level of the respiratory center.

* Diamox, the trade name for acetazoleamide, was made available through the courtesy of Dr. James D. Gallagher, Lederle Division of the American Cyanamid Co., Stamford, Connecticut.

TABLE 1

VENTILATORY RESPONSE TO BREATHING 5 PER CENT CO_2 IN AIR IN FOUR GROUPS

Subject	Age	Sex	B.S.A.	Breathing Mixture: Ambient Air			Breathing Mixture: 5 Per cent CO_2 in Air		
				$\dot{V}_E$* (L./min.)	f† (per min.)	V_T‡ (ml.)	$\dot{V}_E$ (L./min.)	f (per min.)	V_T (ml.)
Group I: Control Subjects									
E. Mc.	52	M	1.79	9.38	19	493	31.90	18	1773
E. C.	22	M	1.74	7.59	17	447	18.40	16	1150
A. O.	55	M	2.02	9.47	17	557	25.90	17	1524
E. A.	48	M	1.88	10.70	22	486	25.00	22	1135
J. A.	19	F	1.39	7.05	22	321	16.40	20	821
W. M.	32	M	1.91	10.90	20	545	29.30	28	1050
J. K.	38	M	1.87	10.80	16	672	30.00	16	1875
A. F.	57	M	1.71	7.58	13	583	16.10	17	945
W. S.	20	M	1.53	9.20	10	920	35.40	18	1965
M. C.	42	F	1.46	5.87	11	533	17.70	16	1104
B. L.	30	M	1.74	9.59	24	400	35.40	22	1610
Average				8.92	17	542	25.59	19	1357
Standard deviation				1.67	5	157	7.42	4	392
Group II: Patients with Chronic Pulmonary Emphysema without CO_2 Retention									
G. E.	63	M	1.71	10.10	26	389	27.30	29	941
G. P.	65	M	1.57	13.40	28	478	30.00	28	1072
P. G.	54	M	1.47	6.50	7	928	17.20	14	1226
J. H.	67	M	1.53	11.00	18	608	23.70	26	910
J. T.	75	M	1.63	7.20	20	360	15.90	18	883
L. T.	39	M	1.91	8.24	12	697	21.20	17	1247
J. S.	39	M	1.69	8.15	19	428	16.20	20	809
T. Ba.	57	M	1.69	8.40	9	933	33.40	15	2228
W. E.	45	M	1.88	12.20	23	531	24.50	23	1065
J. C.	39	M	1.73	9.51	17	560	28.70	27	1062
T. Br.	59	M	1.81	10.10	20	505	20.30	24	846
J. E.	51	M	1.62	8.00	16	500	19.20	19	1038
Average				9.40	18	576	23.13	22	1111
Standard deviation				2.06	2	189	5.77	5	378
Group III: Patients with Chronic Pulmonary Emphysema with CO_2 Retention									
A. P.	53	M	1.57	8.12	24	338	10.40	21	495
A. De.	59	F	1.53	6.92	18	385	7.50	20	375
A. Da.	36	M	1.64	7.28	15	486	13.10	17	771
J. Bu.	45	M	1.47	10.20	22	474	16.60	25	664
A. W.	67	M	1.48	11.50	28	404	19.60	34	576
A. Y.	42	M	1.55	7.25	20	363	10.10	19	532
W. B.	49	M	1.59	10.70	35	306	14.40	31	465
P. M.	52	M	1.70	11.30	28	404	16.90	32	528
B. B.	60	M	1.66	9.74	28	348	17.30	28	614
S. R.	48	M	1.72	9.74	28	348	15.00	40	375
F. P.	63	M	1.76	10.30	20	515	16.30	20	816
J. Be.	58	M	1.59	9.95	20	498	20.40	24	850
J. S.	67	M	1.56	8.30	25	333	14.00	35	400
Average				9.33	24	400	14.74	27	574
Standard deviation				1.47	5	69	3.76	7	162
Group IV: Miscellaneous Patients§									
W. W.	48	M	1.73	8.28	21	394	25.20	20	1260
C. S.	48	M	1.92	11.60	32	363	26.50	27	983
B. B.	63	M	1.88	13.50	35	386	27.40	34	807
N. P.	20	M	1.75	10.20	18	566	39.60	22	1800
G. L.	15	M	1.55	9.09	20	455	35.50	28	1268
E. H.	20	M	1.67	10.80	22	491	37.70	34	1108

* $\dot{V}_E$ = minute ventilation B.T.P.S.
† f = respiratory frequency.
‡ V_T = tidal volume.
§ For diagnosis see text.

The inspired gas mixtures used are indicated in the tables and illustrations. They were administered through an open circuit, using demand valves or an anesthesia bag. Expired gas was collected and measured in a Tissot spirometer from which gas samples were obtained for analysis. Arterial blood was withdrawn anaerobically from an indwelling brachial artery needle during the middle minute of the period of collection of expired gas.

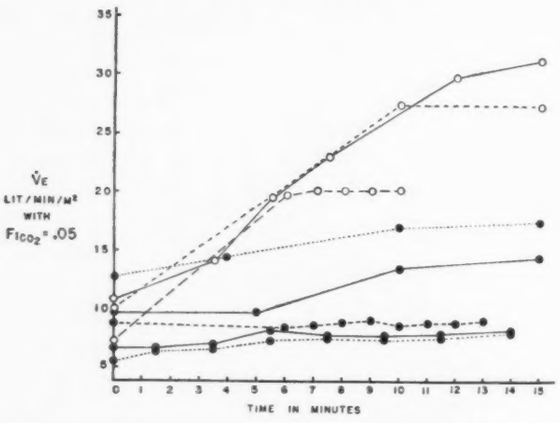

FIG. 1. Graphic representation of the time required for reaching a constant level of ventilation while the patient is breathing a mixture of 5 per cent CO_2 in air; control subjects are indicated by open circles, and patients with pulmonary emphysema and CO_2 retention by closed circles.

All samples were checked in duplicate. The composition of inspired and expired gas was determined using a micro-Scholander apparatus. From these values were calculated the O_2 uptake ($\dot{V}_{O_2}$), CO_2 production ($\dot{V}_{CO_2}$) and respiratory exchange ratio (R_E). Arterial blood samples were analyzed immediately after withdrawal by the method of Van Slyke-Neill for O_2 and CO_2 content and O_2 capacity. Arterial blood pH was determined at constant temperature of 37°C. using the MacInnes-Belcher glass electrode. Arterial blood oxygen tension (P_{aO_2}) was derived from the standard oxyhemoglobin dissociation curve using the value for oxyhemoglobin saturation corrected for pH. The arterial blood carbon dioxide tensions (P_{aCO_2}) were calculated from the line charts of Van Slyke and Sendroy, occasionally supplemented by direct determinations using the bubble method of Riley. The alkali reserve (T_{40}) was expressed as the CO_2 of whole blood at P_{CO_2} of 40 mm. Hg and was obtained from the nomogram of Henderson.

Minute alveolar ventilation ($\dot{V}_A$) was determined as the difference between total minute ventilation ($\dot{V}_E$) and dead space minute ventilation ($\dot{V}_D$). The volume of the respiratory dead space (V_D) for each subject was calculated from the Bohr formula, substituting arterial blood P_{CO_2} for alveolar P_{CO_2}. The measurement of the maximum ventilatory capacity and standard step exercise tests were carried out as previously described.[11] Steady state leg exercise was performed with the patient in the supine position using a pulley system by means of which each leg alternately moved an attached weight a fixed distance.

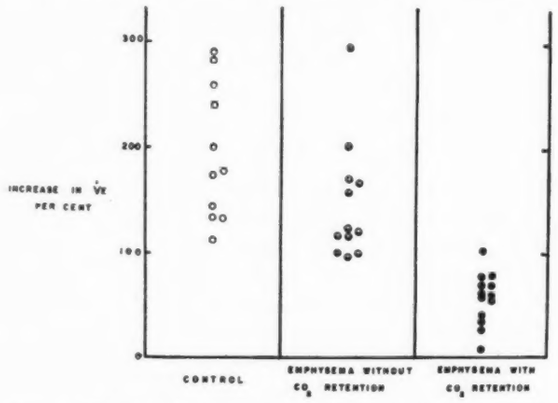

FIG. 2. Chart of the increase in minute ventilation while the patient is breathing a mixture of 5 per cent CO_2 in air in three groups of subjects; for description see text.

RESULTS

1. The ventilatory response to inspired carbon dioxide. The patients were exposed to inspired gas mixtures of 1 per cent, 3 per cent and 5 per cent CO_2 in air. However, statistically significant differences in ventilation became manifest only when the groups were breathing 5 per cent CO_2 in air. The changes in minute ventilation ($\dot{V}_E$), respiratory frequency (f) and tidal volume (V_T) characteristic for each patient while breathing a mixture of 5 per cent CO_2 in air are listed in Table I and illustrated in Figure 2. It is clear that the increase in $\dot{V}_E$ is considerably less in patients with emphysema and CO_2 retention than in the three other groups. Thus mean $\dot{V}_E$ while the patient was breathing a mixture of 5 per cent CO_2 in air exceeded $\dot{V}_E$ while breathing ambient air by 187 per cent in the control group, by 146 per cent in the group of emphysema without CO_2 retention and by 58 per cent in the group of emphysema with CO_2 retention. The data on patients of the fourth group were not averaged because of the hetero-

geneous nature of the disorders represented; however, each of the patients responded as did the normal subjects. The increase in $\dot{V}_E$ in all groups was due primarily to increase in tidal volume (V_T) without statistically significant increase in respiratory frequency (f).

In Figure 3 is further depicted an interesting distinction between the ventilatory responses of the two groups of patients with emphysema. In the emphysema patients with CO_2 retention (Fig. 3A), $\dot{V}_E$ while breathing the mixture of 5 per cent CO_2 in air ($F_{ICO_2} = .05$) is closely related to $\dot{V}_E$ during breathing of ambient air ($F_{ICO_2} = 0$). A similar plot for the emphysematous patients without CO_2 retention is illustrated in Figure 3B, to which the best visual line of Figure 3A has been transposed. It is apparent that in the latter group there is (1) considerable augmentation of $\dot{V}_E$ while breathing the mixture of 5 per cent CO_2 in air and (2) no relation between $\dot{V}_E$ when $F_{ICO_2} = 0$ and $\dot{V}_E$ when $F_{ICO_2} = .05$.

2. Gas exchange in the lungs and arterial blood composition while breathing ambient air and 5 per cent CO_2 in air. In Table II are listed the data concerning respiratory gas exchange and arterial blood gaseous composition during the ventilatory studies listed in Table I. In all groups the respiratory exchange ratio (R_E) decreased during CO_2 breathing. This reflects in large part the lack of sufficient time during the short period of CO_2 breathing to restore fully the dynamic equilibrium for CO_2 throughout the lungs, blood and tissue fluid and indicates some degree of retention of inspired CO_2 in blood and tissues. Under these conditions calculations of the $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ in the lungs do not exactly measure the corresponding exchanges in the tissues, resulting in a higher $\dot{V}_{O_2}$ and lower $\dot{V}_{CO_2}$ than actually obtains.

In normal subjects the arterial blood P_{CO_2} and pH probably can be taken to be a measure of the main chemical stimulus to the respiratory center. It is therefore of interest that, even though the mean changes in arterial blood P_{CO_2} and pH during 5 per cent CO_2 breathing were of the same magnitude in the control subjects and in the two groups of patients with emphysema, being respectively +8, +8 and +7 mm. Hg and −0.6, −0.6 and −0.4 pH units (Table II), the patients with emphysema and CO_2 retention had a consistently lower ventilatory response to the inspired CO_2 mixture. Further analysis, relating arterial blood P_{CO_2} to alveolar ventilation ($\dot{V}_A$) rather than to minute ventilation ($\dot{V}_E$), indicates that in the emphysematous patient with CO_2 retention the increase in $\dot{V}_A$ is generally less than in the other control subjects and patients. This is illustrated in Figure 4. Finally, no relationship could be

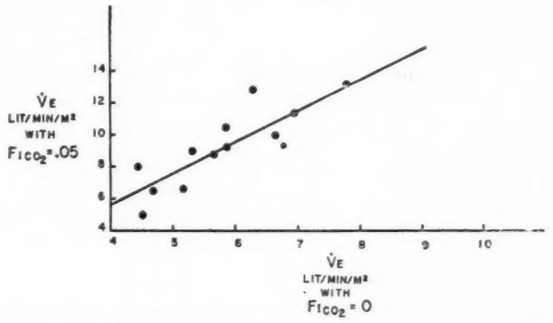

FIG. 3A. Correlation between minute ventilation while the patient is breathing ambient air and while breathing 5 per cent CO_2 in air in thirteen patients with pulmonary emphysema and CO_2 retention; the regression line is the best visual line through the points.

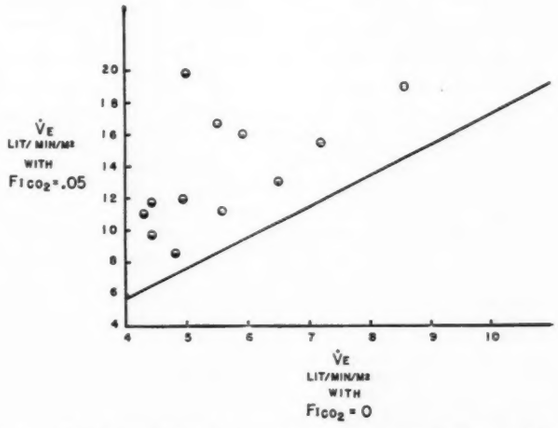

FIG. 3B. Correlation between minute ventilation while the patient is breathing ambient air and while breathing 5 per cent CO_2 in air in twelve patients with pulmonary emphysema without CO_2 retention. The visual line of Figure 3A has been included to facilitate comparison between the two groups of patients.

established between the level of alkali reserve (T_{4C}) and the ventilatory response to 5 per cent CO_2 in air.

3. Effect of relief or aggravation of hypoxia on the ventilatory response to 5 per cent CO_2 in air. As a result of a limited increase in $\dot{V}_A$ while breathing 5 per cent CO_2 in air the patients with emphysema and CO_2 retention exhibited a slight rise in arterial blood oxyhemoglobin saturation (Table II) and oxygen tension (P_{aO_2}), the increments varying with the level of arterial oxyhemoglobin saturation prior to CO_2 breath-

TABLE II

GAS EXCHANGE AND ARTERIAL BLOOD COMPOSITION WHILE BREATHING AMBIENT AIR AND 5 PER CENT CO_2 IN AIR IN FOUR GROUPS

Subject	Breathing Mixture: Ambient Air						Breathing Mixture: 5% CO_2 in Air					
	Gas Exchange in Lungs			Arterial Blood			Gas Exchange in Lungs			Arterial Blood		
	$\dot{V}_{O_2}$* (L./min./M²)	$\dot{V}_{CO_2}$† (L./min./M²)	R_E‡	O_2 (sat. %)	P_{CO_2} (mm. Hg)	pH	$\dot{V}_{O_2}$ (L./min./M²)	$\dot{V}_{CO_2}$ (L./min./M²)	R_E	O_2 (sat. %)	P_{CO_2} (mm. Hg)	pH
Group I: Control Subjects												
E. Mc.	131	112	.86	94	37	7.43	144	96	.68	96	45	7.39
E. C.	138	109	.79	96	39	7.43	163	109	.67	99	41	7.41
A. O.	122	107	.88	98	35	7.42	140	96	.69	98	42	7.36
E. A.	127	113	.89	94	37	7.42	135	117	.80	99	47	7.35
J. A.	140	121	.86	94	35	7.47	145	121	.83	97	46	7.38
W. M.	143	126	.88	93	36	7.41	173	120	.70	98	45	7.33
A. F.	146	130	.89	96	44	7.43	125	101	.80	100	50	7.39
J. K.	146	144	.98	97	38	7.40	143	125	.87	96	46	7.35
W. S.	216	167	.77	95	37	7.43	226	170	.76	100	45	7.37
M. C.	148	113	.76	95	31	7.48	.....	.....	...	.....	.....	...
B. L.	132	102	.78	95	33	7.42	.....	.....	...	.....	.....	...
Average	144	122	.85	95	37	7.43	154	117	.76	98	45	7.37
Standard deviation	26.6	19.4	.05	1.4	3.2	.02	28.5	22.5	.02	1.4	2.5	.02
Group II: Patients with Chronic Pulmonary Emphysema without CO_2 Retention												
G. E.	130	107	.82	90	40	7.40	153	118	.77	96	43	7.38
G. P.	152	126	.83	90	40	7.39	167	109	.65	99	47	7.33
P. G.	110	93	.85	93	43	7.40	167	101	.60	95	56	7.34
J. H.	135	112	.83	95	43	7.40	139	105	.76	100	50	7.37
J. T.	136	122	.89	95	43	7.42	153	106	.69	100	49	7.38
L. T.	146	123	.84	95	39	7.46	174	114	.66	100	54	7.31
J. S.	131	117	.88	92	41	7.38	131	83	.64	99	52	7.29
T. Ba.	153	135	.89	96	36	7.41	152	124	.82	99	42	7.37
W. E.	156	133	.85	93	39	7.41	157	113	.73	95	45	7.37
J. C.	149	120	.79	94	36	7.43	160	108	.68	97	45	7.32
T. Br.	153	138	.90	95	40	7.42	139	108	.78	99	47	7.38
J. E.	151	123	.82	96	37	7.44	140	97	.70	100	47	7.36
Average	142	121	.85	94	40	7.41	153	107	.71	98	48	7.35
Standard deviation	13.1	15.7	.03	2.0	2.6	.02	12.7	10.1	.06	1.9	4.1	.03
Group III: Patients with Chronic Pulmonary Emphysema with CO_2 Retention												
A. P.	122	115	.95	83	50	7.43	125	87	.70	90	52	7.40
A. De.	120	112	.86	86	59	7.37	100	77	.78	92	66	7.35
A. Da.	138	124	.90	87	48	7.39	149	112	.75	94	58	7.31
J. Bu.	132	113	.86	85	50	7.43	184	113	.61	92	54	7.36
A. W.	158	147	.93	88	54	7.40	166	143	.87	91	60	7.36
A. Y.	110	100	.91	74	66	7.30	175	126	.72	84	70	7.30
W. B.	148	135	.91	86	58	7.39	140	115	.82	92	62	7.38
P. M.	157	128	.82	77	56	7.36	.....	.....	...	93	60	7.32
B. B.	157	127	.81	88	52	7.39	154	112	.72	97	64	7.33
S. R.	152	140	.92	78	63	7.37	149	117	.79	91	68	7.35
F. P.	137	109	.80	82	47	7.39	164	97	.69	95	57	7.35
J. Be.	158	139	.88	93	46	7.40	166	127	.77	100	51	7.37
J. S.	140	132	.95	85	59	7.36	143	103	.72	92	66	7.27
Average	141	125	.88	84	54	7.38	151	111	.75	93	61	7.34
Standard deviation	12.4	13.5	.04	1.6	6.1	.03	21.9	15.5	.06	3.6	5.9	.03
Group IV: Miscellaneous Patients												
W. W.	117	99	.86	96	36	7.43	130	95	.73	100	43	7.36
C. S.	158	122	.78	84	38	7.49	166	121	.74	95	48	7.43
B. B.	150	127	.85	92	37	7.43	164	116	.71	95	51	7.37
N. P.	138	128	.92	91	35	7.42	169	118	.70	95	39	7.38
G. L.	166	139	.79	84	37	7.44	179	118	.66	82	43	7.33
E. H.	158	126	.80	93	41	7.40	206	128	.62	99	50	7.33

* $\dot{V}_{O_2}$ = oxygen uptake S.T.P.D.

† $\dot{V}_{CO_2}$ = carbon dioxide output S.T.P.D.

‡ R_E = respiratory exchange ratio in the lungs.

ing. It was therefore necessary to estimate the contribution of a reduction in the hypoxic stimulus to the diminished ventilatory response to inspired CO_2 in these patients. Two series of experiments were devised.

a. Fourteen emphysematous patients with

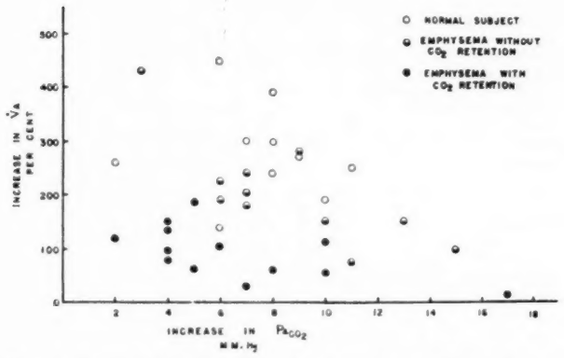

FIG. 4. Correlation between the increase in arterial blood CO_2 tension and the increase in alveolar ventilation in the three groups of subjects while breathing 5 per cent CO_2 in air; for discussion see text.

CO_2 retention and arterial oxyhemoglobin unsaturation were allowed to breathe a mixture of either 25 per cent or of 16 per cent O_2 in N_2. While breathing the 25 per cent O_2 mixture, mean P_{aO_2} increased from 48 to 65 mm. Hg but there was no associated change in $\dot{V}_E$; conversely, with the 16 per cent O_2 mixture a decrease in mean P_{aO_2} from 62 to 38 mm. Hg effected only a slight increase in V_E. (Table III.)

TABLE III

EFFECTS OF CHANGES IN ARTERIAL BLOOD OXYGEN TENSION ON MINUTE VENTILATION IN PATIENTS WITH CHRONIC PULMONARY EMPHYSEMA AND CO_2 RETENTION

FIO_2*	No. of Studies	Average Arterial (% HbO_2)	Average P_{aO_2}† (mm. Hg)	Average P_{aCO_2}‡ (mm. Hg)	$\dot{V}_E$§ (L./min./M^2)
.21	8	79	48	55	5.5
.25	8	89	65	55	5.5
.21	6	91	62	50	8.6
.16	6	72	38	49	9.2

* FIO_2 = oxygen concentration in inspired gas.
† P_{aO_2} = oxygen partial pressure in arterial blood.
‡ P_{aCO_2} = carbon dioxide partial pressure in arterial blood.
§ $\dot{V}_E$ = minute ventilation B.T.P.S.

b. The patients of the three groups breathed successively (1) ambient air, (2) a mixture of 5 per cent CO_2 in air and (3) a mixture of 5 per cent CO_2 and 14 per cent O_2 in N_2, or a mixture of 5 per cent CO_2 in 95 per cent O_2. The changes in arterial blood P_{CO_2} while breathing the various 5 per cent CO_2 mixtures were similar in all three groups. (Table IV.) It is apparent that while breathing 5 per cent CO_2 the role of the moderate hypoxic stimulus in the control group and in the group with emphysema and CO_2 retention is negligible. However, when 5 per cent CO_2 was administered in 95 per cent O_2 a significant reduction in $\dot{V}_E$ occurred only

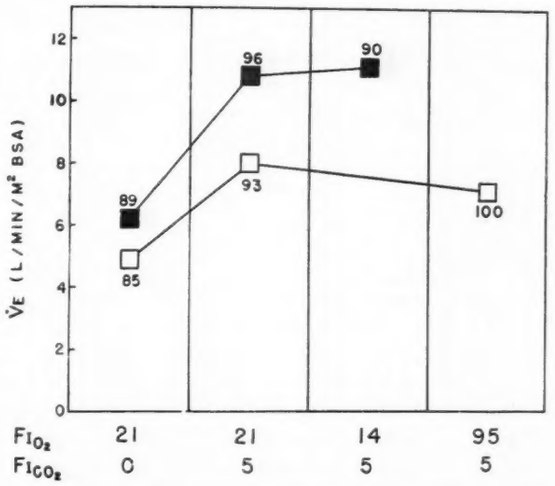

FIG. 5. Schematic representation of the average effect of breathing 5 per cent CO_2 with various mixtures of O_2 upon the minute ventilation in two series of observations on patients with chronic pulmonary emphysema and CO_2 retention. The figures next to the symbols represent the arterial blood O_2 saturation obtained with the various mixtures of inspired gas; each solid block represents the average of seven observations; each open block represents the average of five observations.

in the patients with emphysema and CO_2 retention. The average results of these studies in the patients with emphysema and CO_2 retention are illustrated in Figure 5.

In summary, a moderate relief of the hypoxic stimulus cannot account for the diminished ventilatory response characteristically observed in emphysematous patients with CO_2 retention during CO_2 breathing. On the other hand, increase in arterial blood P_{O_2} to levels far in excess of the physiologic range is capable of causing a marked diminution in $\dot{V}_E$. Such levels may result from pure oxygen breathing but are certainly not attainable while breathing 5 per cent CO_2 in air.

4. Effect of diminished ventilatory capacity on the ventilatory response to breathing 5 per cent CO_2 in air and to exercise. In each of the patients with emphysema and CO_2 retention the voluntary maximum breathing capacity (MBC) was considerably reduced. In six patients of this group the average increase in $\dot{V}_E$ while breathing the mixture of 5 per cent CO_2 in air was compared to the increase in $\dot{V}_E$ during a

standard exercise test and to the MBC. (Table v.) The data show that the $\dot{V}_E$ while the patient was breathing 5 per cent CO_2 increased only slightly above the control level and failed to reach a level higher than one-third of the MBC; by way of contrast, the $\dot{V}_E$ during mild exercise reached two-thirds of the MBC. This disparity in response to CO_2 and exercise stimuli was repeatedly demonstrated in these patients, not only during brief periods of exercise but also during more prolonged periods of steady state exercise, the results of which are not tabulated. On the other hand, in some patients with emphysema without CO_2 retention who showed a considerable reduction in MBC, $\dot{V}_E$ while the patient was breathing 5 per cent CO_2 reached the level of ventilation obtained during the MBC test. In patient P. G., for instance, the MBC was 17.0 liters per minute, whereas $\dot{V}_E$ during 5 per cent CO_2 breathing was 17.9 liters per minute. Therefore, in patients with emphysema without CO_2 retention the MBC may constitute the limit of increase in V_E during CO_2 breathing; in this group an apparent reduction in responsiveness of the respiratory center to the CO_2 stimulus would, in fact, be due to restricted function of the chest bellows.

TABLE IV

COMBINED EFFECTS OF VARIATIONS IN ARTERIAL BLOOD O_2 SATURATION AND CARBON DIOXIDE PARTIAL PRESSURE UPON VENTILATORY DRIVE IN THREE GROUPS

Inspired Gas Mixture	Group I: Control				Group II: Emphysema without CO_2 Retention				Group III: Emphysema with CO_2 Retention			
	No. of Experiments	Arterial Blood		$\dot{V}_E$† (L./min./M²)	No. of Experiments	Arterial Blood		$\dot{V}_E$ (L./min./M²)	No. of Experiments	Arterial Blood		$\dot{V}_E$ (L./min./M²)
		O_2 (sat. %)	P_{CO_2}* (mm. Hg)			O_2 (sat. %)	P_{CO_2} (mm. Hg)			O_2 (sat. %)	P_{CO_2} (mm. Hg)	
Ambient air.	8	96	37	5.31	..	...	..	.....	5	89	49	6.23
5% CO_2 in air.....	8	98	44	14.70	..	...	..	.....	5	96	56	10.80
5% CO_2 in 14% O_2...	8	95	42	15.10	..	...	..	.....	5	90	54	11.10
Ambient air.	3	95	36	5.59	4	95	40	5.07	7	85	52	4.89
5% CO_2 in air.....	3	99	46	16.10	4	99	50	14.00	7	93	61	7.98
5% CO_2 in 95% O_2...	3	100	46	16.20	4	100	49	13.30	7	100	62	6.59

* P_{CO_2} = partial pressure of carbon dioxide.
† $\dot{V}_E$ = minute ventilation B.T.P.S.

TABLE V

VENTILATORY RESPONSE TO DIFFERENT STIMULI IN PATIENTS WITH CHRONIC PULMONARY EMPHYSEMA AND CO_2 RETENTION

Subject	Maximum Voluntary Breathing Capacity (L./min.)	Minute Ventilation		
		Ambient Air* (L./min.)	5% CO_2 in Air* (L./min.)	Ambient Air† (L./min.)
A. P.	30.0	8.1	10.4	20.0
A. Da.	38.0	7.3	13.1	17.8
B. B.	26.0	9.7	17.3	21.0
W. B.	67.0	10.7	14.4	22.6
A. Y.	27.0	7.2	10.1	13.7
A. Da.	32.0	6.9	7.5	18.0
Average	37.0	8.3	12.1	19.0

* At rest.
† During one minute exercise.

5. The effect of change in alkali reserve on the sensitivity of the respiratory center. In preliminary trials with oral administration of large doses of ammonium chloride and sodium bicarbonate to normal subjects it was not possible to cause a sustained change in alkali reserve. On the other hand, in a prolonged study of the effect of daily administration of 500 mg. of the carbonic anhydrase inhibitor diamox to seven patients with emphysema and CO_2 retention it was possible to assay the role of a reduction in alkali reserve upon the ventilatory response to inspired CO_2. The results in five of these seven patients have been presented briefly elsewhere.[11b]

TABLE VI

EFFECTS OF BREATHING 5 PER CENT CO_2 IN AIR ON ARTERIAL BLOOD COMPOSITION AND MINUTE VENTILATION FOLLOWING REDUCTION IN THE ALKALI RESERVE (T_{40}), IN SEVEN PATIENTS WITH CHRONIC PULMONARY EMPHYSEMA AND CO_2 RETENTION

Date	Therapy	T_{40} (vol. %)	Breathing Mixture: Ambient Air			Breathing Mixture: 5% CO_2 in Air			$\frac{\dot{V}_{E(2)} - \dot{V}_{E(1)}}{\dot{V}_{E(1)}} \times 100$
			Arterial Blood		$\dot{V}_{E(1)}$ (L./min.)	Arterial Blood		$\dot{V}_{E(2)}$ (L./min.)	
			P_{CO_2} (mm. Hg)	O_2 (sat. %)		P_{CO_2} (mm. Hg)	O_2 (sat. %)		
Subject 1, A. P.									
11/19/52	Control	61	50	83	8.12	52	90	10.40	61
11/26/52	Control	56	56	84	7.77	60	91	11.50	56
12/3/52	Diamox	48	47	83	8.40	58	89	9.94	48
12/11/52	Diamox	49	53	90	6.97	61	89	8.86	49
12/29/52	Diamox	52	43	87	9.08	56	89	11.20	52
1/22/53	Diamox	48	46	91	8.27	56	97	10.60	48
2/9/53	Diamox	49	40	96	9.22	50	97	13.70	49
3/11/53	Diamox	49	43	94	9.96	50	100	13.50	49
4/29/53	Diamox	43	43	91	8.15	54	95	12.00	43
9/15/53	Diamox	47	43	81	8.35	52	90	11.00	47
11/17/53	Diamox	45	45	87	8.60	54	100	12.70	45
1/13/54	Control	55	54	73	9.95	61	92	13.80	55
Subject 2, A. W.									
12/22/52	Control	60	54	88	11.50	60	91	19.60	70
12/24/52	Control	..	..	..	11.70	..	...	15.70	34
12/31/52	Diamox	53	45	87	10.50	56	92	16.30	55
1/15/53	Diamox	53	48	88	11.00	60	94	16.10	46
1/21/53	Diamox	50	48	87	12.10	59	94	17.60	46
2/19/53	Diamox	52	57	84	9.38	64	94	13.80	47
3/5/53	Diamox	52	46	87	11.60	52	97	14.80	28
3/9/53	Diamox	50	47	88	12.20	56	93	16.00	31
4/27/53	Diamox	49	43	93	12.70	52	94	17.00	34
10/6/53	Diamox	52	54	87	9.57	63	94	13.50	41
Subject 3, A. Y.									
1/7/53	Control	56	66	74	7.25	70	84	10.10	40
2/19/53	Control	57	54	60	6.54	..	...	9.05	38
6/17/53	Diamox	48	48	84	6.70	57	95	9.72	45
11/24/53	Diamox	48	55	78	5.19	70	85	8.20	57
12/16/53	Diamox	47	51	85	6.12	59	94	8.39	37
1/31/55	Diamox	49	53	80	5.75	60	88	7.30	27
Subject 4, P. M.									
3/27/53	Control	59	54	68	11.30	..	...	16.90	50
4/8/53	Diamox	52	56	77	11.50	60	93	14.30	25
5/8/53	Diamox	49	43	74	12.20	53	85	17.60	44
5/18/53	Diamox	..	..	..	11.40	..	...	17.40	53
Subject 5, B. B.									
11/2/53	Control	53	52	88	9.74	64	97	17.30	77
1/19/54	Diamox	46	47	89	9.20	58	95	15.60	69
2/11/55	Diamox	41	39	93	8.97	50	98	10.97	22
Subject 6, W. B.									
1/26/53	Control	59	58	86	10.70	62	92	14.40	35
2/4/53	Control	55	50	87	11.70	58	94	13.30	12
2/20/53	Diamox	48	50	90	10.00	58	96	14.50	45
3/16/53	Diamox	47	46	91	12.40	50	95	19.00	53
4/8/53	Diamox	47	47	94	9.10	60	99	16.70	83
5/27/53	Diamox	48	45	94	8.12	54	97	14.10	74
Subject 7, A. De.									
11/21/52	Control	54	59	85	6.92	66	92	7.50	8
11/24/52	Control	55	54	87	6.72	60	96	9.20	37
5/21/53	Diamox	46	60	86	6.38	70	96	9.20	39
9/16/53	Diamox	54	56	88	5.17	62	92	9.46	83
11/25/53	Diamox	46	49	85	5.72	54	97	10.40	82
12/15/53	Diamox	48	53	86	5.26	59	96	8.37	59
2/10/55	Diamox	51	48	83	6.50	53	95	9.50	46

Serial measurements presented in Table VI for these seven patients indicate that there was, in all instances, a sustained reduction in alkali reserve to normal or nearly normal levels; there was also a less consistent reduction in arterial blood P_{CO_2} and a variable increase in arterial blood oxyhemoglobin saturation. Statistical analysis of the data collected prior to and during diamox therapy in this small group of patients showed (1) a decrease in mean arterial blood T_{40} from 57 vol. per cent (S.D. $\pm$ 2.8 vol. per cent) during the control period to 49 vol. per cent (S.D. $\pm$ 2.8 vol. per cent) during treatment, (2) a decrease in mean arterial blood P_{CO_2} from 55 mm. Hg (S.D. $\pm$ 4.4 mm. Hg) to 48 mm. Hg (S.D. $\pm$ 5.1 mm. Hg) and (3) an increase in mean arterial blood oxyhemoglobin saturation from 80 per cent (S.D. $\pm$ 9.3 per cent) to 87 per cent (S.D. $\pm$ 5.1 per cent). All these differences are statistically significant for $P < .01$.

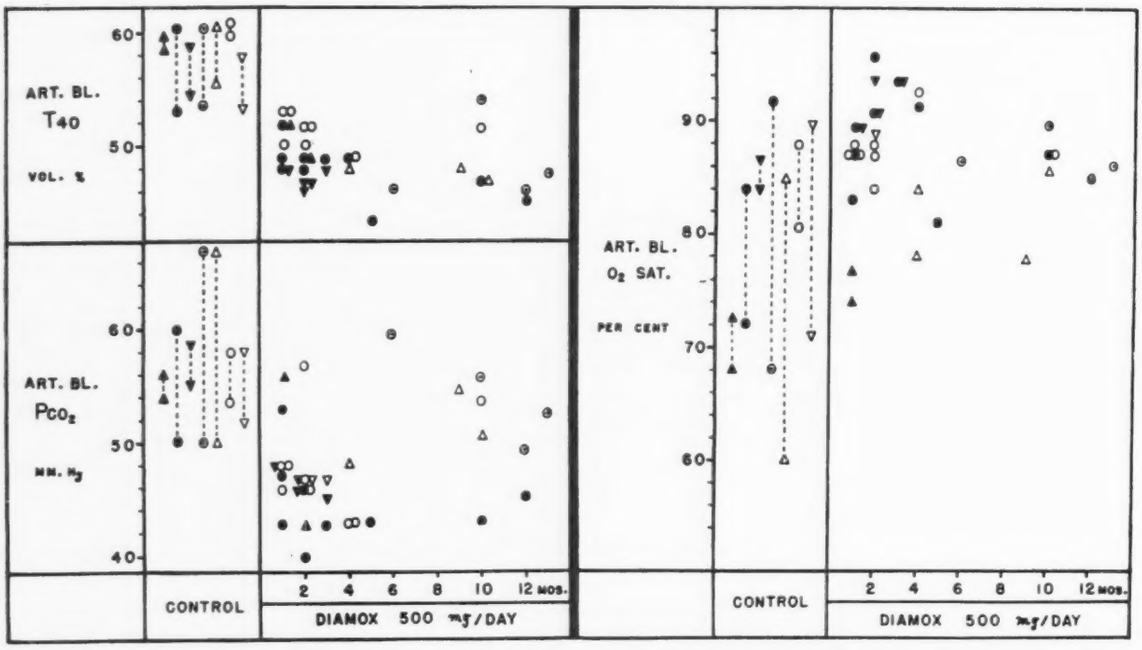

FIG. 6. Chart of the effect of diamox therapy upon the arterial blood alkali reserve, CO_2 tension and oxyhemoglobin saturation in seven patients with pulmonary emphysema and CO_2 retention. In the control box the range of variation during the year preceding diamox therapy is indicated by broken lines connecting the separate symbols designating each patient.

In Figure 6 are plotted the consecutive changes in the alkali reserve (T_{40}), arterial blood P_{CO_2} and oxyhemoglobin saturation during the first year of diamox therapy. In this illustration the data of Table VI have been supplemented by inclusion of the range of arterial blood values for each patient during the year prior to diamox therapy. It is clear that arterial blood P_{CO_2} and T_{40} decreased during treatment with diamox. However, levels of the P_{CO_2} in arterial blood fluctuated somewhat during treatment. It is therefore pertinent to note that the arterial blood samples were drawn for analysis at varying time intervals after the daily dose of diamox, although usually they were drawn twenty-four hours later. Consequently it is to be anticipated that blood samples drawn within a few hours after ingestion of diamox and at the height of metabolic acidosis would have the highest P_{CO_2}; conversely, blood samples drawn twenty-four hours after a given dose of diamox, when arterial blood pH had returned virtually to normal levels, would have the lowest P_{CO_2}. The fluctuations in arterial blood P_{CO_2}, which have been observed by others[11c,11d] when the drug was given in divided doses, may therefore in fact be due to the sampling of blood at a time when the acute metabolic acidosis caused by diamox is still at its height. Despite these qualifications, the trend to reduction in arterial blood P_{CO_2} is unmistakable.

In five of the seven patients the increase in $\dot{V}_E$ while breathing 5 per cent CO_2 in air remained during diamox therapy within the pretreatment range. In only two of the patients

was the increase in $\dot{V}_E$ somewhat greater during diamox therapy than before. However, even in these two patients the increase in $\dot{V}_E$ remained substantially less than in either the control subjects or the patients with emphysema without CO_2 retention. A diagram illustrating the trend of changes usually observed during the prolonged periods of observation is presented for patient A. P. in Figure 7.

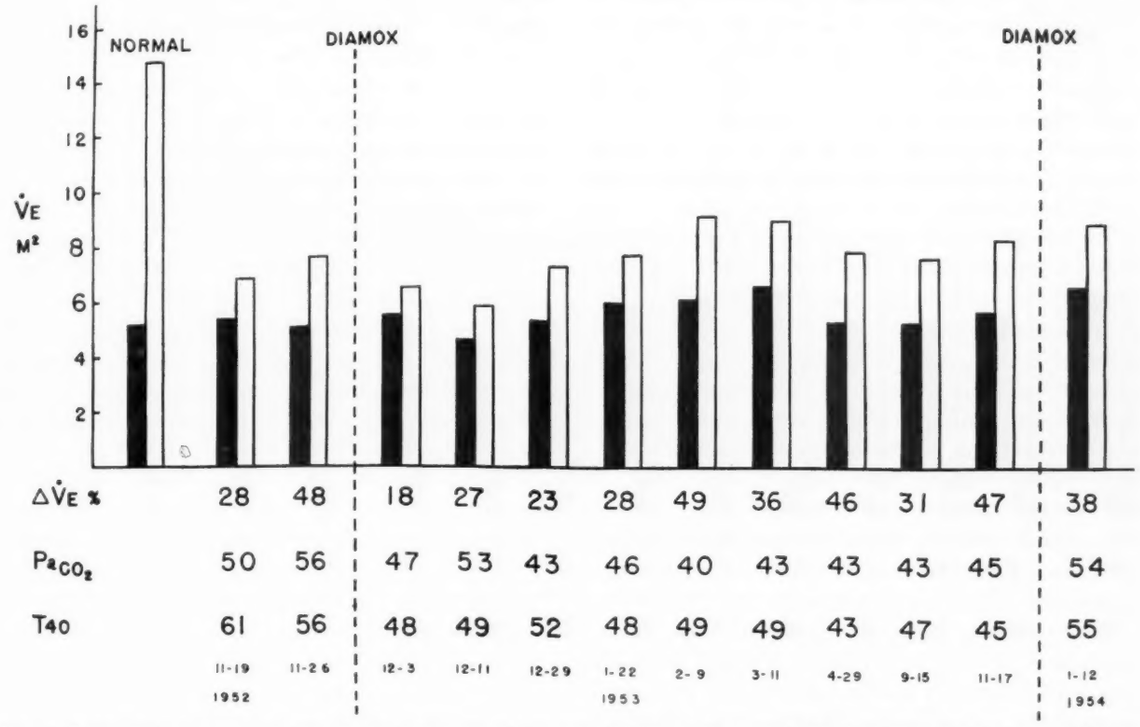

FIG. 7. Schematic representation of the influence of the arterial blood P_{CO_2} and alkali reserve upon the ventilatory response in patient A. P. before, during and after diamox therapy. Solid block represents the minute ventilation while breathing ambient air; open block represents the minute ventilation while breathing 5 per cent CO_2 in air; data obtained during diamox therapy are within the two broken vertical lines.

A statistical analysis of the increments in $\dot{V}_E$ while breathing the 5 per cent CO_2 mixture in these seven patients indicates a mean increase of 46 per cent (S.D. $\pm$ 20.2 per cent) prior to diamox therapy and 48 per cent (S.D. $\pm$ 15.3 per cent) during treatment. The difference between these values is not statistically significant for $P < .1$.

COMMENTS

The results of these studies may be considered from two points of view: (1) their contribution to the understanding of the factors involved in the regulation of ventilation and (2) their application to the development of a rational therapeutic program for the prevention and management of CO_2 retention occurring in the course of chronic pulmonary emphysema.

I. Factors Regulating Ventilation

The generally accepted concept of the function of the normal respiratory center portrays a stream of stimuli from diverse sources converging upon this center to be integrated into the efferent motor responses which constitute the normal ventilatory drive. These stimuli arise primarily (1) from the variations of carbon dioxide tension (P_{aCO_2}) or pH in the arterial blood acting directly upon the respiratory center, (2) from the variations of the oxygen tension in the arterial blood (P_{aO_2}) acting upon the chemoreceptors in the aortic and carotid bodies, (3) from the stretching of strategically located proprioceptors in the chest cage, the respiratory muscles, the lungs and the limbs and (4) from higher centers such as the cerebral cortex. In the normal resting subject an increase in arterial blood P_{CO_2} is the prime stimulus for augmentation of ventilation; by way of contrast, among patients with chronic pulmonary emphysema included in the present study is a group in

whom responsivesness to this stimulus is diminished. This study therefore makes possible an evaluation of other respiratory stimuli which are usually considered to play lesser roles in the regulation of ventilation.

A. Increase in Arterial Blood CO_2 Tension (P_{aCO_2}). It is beyond the scope of this paper to define the arterial blood P_{CO_2} stimulus as distinct from arterial or intracellular hydrogen ion concentration. However, under the conditions of these experiments the P_{aCO_2} must reflect, even if it does not quantitatively measure, the stimulus applied to specialized receptors in the cells of the respiratory center.

In the group of patients with chronic pulmonary emphysema and CO_2 retention, the sluggish response of the respiratory center to the P_{aCO_2} stimulus can be recognized by the slight increase in ventilation attending the artificial increase in P_{aCO_2} and by a resting minute ventilation, while breathing ambient air, which was lower than in the group of patients with emphysema without CO_2 retention. Indeed, in the group with CO_2 retention the minute ventilation while breathing ambient air is least in those patients in whom the ventilatory response to inspired CO_2 is most diminished.

The mechanisms underlying the diminished sensitivity of the respiratory center have not been uncovered by the present study; however, among the possible factors investigated three warrant further consideration: (1) Damage to the respiratory center during a period of particularly marked acute hypoxemia. Such acute episodes are often encountered in the course of the disease. It has been demonstrated in this and in other studies[12] that chronic hypoxemia, such as occurs in congenital heart disease, does not impair the ventilatory response to inspired CO_2. However, since nervous tissue is particularly susceptible to injury by severe hypoxemia, the possibility remains that acute episodes of bronchitis and bronchopneumonia may reduce arterial blood P_{O_2} to levels capable of causing permanent damage to some specialized cells of the respiratory center. (2) Prolonged hypercarbia. The extended stay of normal subjects in an environment enriched with CO_2 is known to impair the sensitivity of the respiratory center to the CO_2 stimulus[13] but sensitivity is restored after withdrawal from this noxious environment. However, since experiments in normal subjects have been concerned with exposure to ambient CO_2 limited to a few days, it cannot be stated whether or not more prolonged exposure would cause irreversible damage to the respiratory center. (3) Increase in alkali reserve. The level of the alkali reserve, as adjusted by the kidney and the body tissues in compensation for persistent alteration in arterial blood P_{CO_2}, may condition the ventilatory response to the CO_2 stimulus. Thus chronic reduction in alkali reserve, such as follows hyperventilation at altitude, is associated with an augmented sensitivity to P_{aCO_2}.[14,15] Furthermore, perfusion experiments in animals indicate that changes in the carbonic acid-bicarbonate ratio of cerebrospinal fluid may alter the ventilatory response.[8] Observations such as these constitute a basis for the suggestion that the impaired ventilatory response to inspired CO_2 in patients with pulmonary emphysema and carbon dioxide retention may be due to increase in alkali reserve.[4] However, in the present study reduction in alkali reserve resulting from long-term administration of the carbonic anhydrase inhibitor sulfacetamide (diamox) failed to demonstrate any consistent restoration of sensitivity of the respiratory center to inspired CO_2. The irreversibility of this depressed state will be discussed in greater detail subsequently.

B. Decrease in Arterial Blood O_2 Tension (P_{aO_2}). In normal subjects a decrease in arterial blood O_2 tension accomplished by reducing the O_2 content of inspired gas results in only a slight increase in minute ventilation ($\dot{V}_E$). The present study explored the possibility that, in the face of a reduction in the effectiveness of arterial blood P_{CO_2} as a ventilatory stimulus, a heightened sensitivity to a decrease in P_{aO_2} might exist; no evidence could, however, be adduced to support this premise. Indeed, patients with pulmonary emphysema and CO_2 retention respond as do normal subjects, since they experience little change in $\dot{V}_E$ in response to either aggravation of hypoxemia or restoration of P_{aO_2} to within physiologic range. However, as anticipated from earlier studies,[16,17] a considerable increase in P_{aO_2} and therefore of O_2 dissolved in plasma, such as occurs during breathing of 100 per cent O_2, elicits a marked decrease in $\dot{V}_E$.

In brief, within the range of variations in arterial blood P_{O_2} observed during ambient air breathing by both normal subjects and patients with pulmonary emphysema, the hypoxic stimulus appears to contribute little to the total ventilatory drive.

C. Proprioceptors in the Chest, Respiratory Muscles

and Lungs. A striking difference exists between the minute ventilation of patients with chronic pulmonary emphysema and CO_2 retention on the one hand and patients with diffuse pulmonary disease presenting the syndrome of alveolar-capillary block[18] on the other. In the latter group hyperventilation is considerable at rest, even though arterial hypoxemia may be absent and despite the presence of normal or reduced P_{aCO_2}. The initiation of this hyperventilation in the absence of adequate chemical stimuli has been ascribed to an excess of stretch stimuli initiated by the diffuse pulmonary disease; its persistence may then be due to an increase sensitivity of the respiratory center to arterial blood P_{CO_2} brought about by the reduction in alkali reserve which occurs as renal compensation for persistent hyperventilation. In sharp contrast, hyperventilation may not occur in patients with pulmonary emphysema and CO_2 retention as the disease progresses, despite arterial hypoxemia and increased P_{aCO_2}. Obviously, proprioceptive reflexes arising from chest, respiratory muscles and lungs do not compensate for the diminished effectiveness of the arterial blood P_{CO_2} stimulus.

D. Proprioceptors in Limbs. It is well established that in normal subjects the increase in minute ventilation ($\dot{V}_E$) during exercise cannot be accounted for by the summation of known chemical stimuli.[19,20] The present study confirms the concept that during exercise there is a dissociation between limb stimuli and known chemical stimuli, since patients poorly responsive to an increase in arterial blood P_{CO_2} had, nonetheless, a marked increase in $\dot{V}_E$ during either a short standard exercise or a mild steady state exercise.

II. The Prevention and Control of CO_2 Retention

A. Noxious Effects of CO_2 Retention. The noxious influence of CO_2 retention on the evolution of chronic pulmonary emphysema may be considered under three headings: (1) physical, that is, the reciprocal effect on alveolar O_2 tension of an elevation of alveolar CO_2 tension; (2) physiologic, that is, the irreversible reduction in responsiveness of the respiratory center to one of its most potent stimuli and the renal compensation for respiratory acidosis, and (3) pharmacologic, that is, the action of increased CO_2 tension as a depressant of physiologic and mental processes, which occasionally progresses to the stage of narcosis and death.

1. *Physical:* It has been recently suggested[21] that the development of CO_2 retention during the course of chronic pulmonary emphysema might operate as a compensatory mechanism, teleologically directed at reducing the O_2 cost of ventilation, thereby increasing the amount of O_2 available for non-ventilatory work. Although this concept is intriguing in principle, it should be borne in mind that an elevation in alveolar P_{CO_2} while breathing CO_2-free air would, *per se*, cause a reduction in alveolar and arterial P_{O_2}, thereby requiring a series of compensating circulatory and tissue mechanisms in order to ensure adequate O_2 transport and utilization.

2. *Physiologic:* From these studies emerges the essential finding that the adverse physiologic effect of CO_2 retention upon the respiratory center, once established, is generally not reversible. A similar conclusion had previously been reached by indirect estimates of blood gas composition and shorter periods of clinical observation.[5] As a consequence, the automatic and adequate augmentation of alveolar ventilation, a prime compensatory mechanism for the disturbed alveolar ventilation-perfusion relationships which characterize pulmonary emphysema, is denied to the patient with this disease. However, the impaired ventilatory response to arterial blood P_{CO_2} is not the only factor limiting alveolar ventilation ($\dot{V}_A$); in planning an adequate therapeutic program it is obviously necessary to distinguish between a limitation in $\dot{V}_A$ due to this mechanism and that due to mechanical restriction of the chest bellows.

At this point it is perhaps worthwhile to stress that the problem of restoring the CO_2 content as well as the partial pressure of CO_2 to normal limits in these patients is of considerable magnitude. This difficulty stems from two facts: (1) The body tissue fluid supplements the circulating blood in constituting an enormous reservoir for CO_2, and (2) the regulation of the CO_2 content of this reservoir depends not only upon the lungs but also upon the action of the kidneys in controlling the reabsorption of bicarbonate and associated cations and the availability of tissue buffer base.[22] The interrelation between lung and kidney is emphasized in the demonstration that a high P_{aCO_2} such as may result from inadequate alveolar ventilation, is an essential stimulus leading to augmentation of the alkali reserve by the kidney.[22–24] The mechanism whereby the alkali reserve may be reduced during diamox therapy is quite clear; however, the

means by which arterial blood P_{CO_2} is concomitantly reduced is not as readily demonstrable. The most likely cause of reduction in the arterial blood P_{CO_2} and of increase in arterial blood oxyhemoglobin saturation is an improvement in alveolar ventilation. This mechanism has been predicated by others.[11c,11d] However, in the present study calculations of $\dot{V}_A$ from the O_2 uptake, respiratory exchange ratio and arterial blood P_{CO_2} before and after diamox therapy do not reveal a consistent increase. However, this result may be misleading since, according to the calculations employed, a drop in arterial blood P_{CO_2} of 5 mm. Hg (about twice the error of the technic) would result in an increase in calculated $\dot{V}_A$ of only approximately 10 per cent. Therefore it is possible that increases in $\dot{V}_A$, undetectable at the time of study, may have occurred. The mechanism whereby such an increase in $\dot{V}_A$ would be accomplished remains obscure, since it has not been possible to demonstrate increased responsiveness of the respiratory center to the CO_2 stimulus.

3. *Pharmacologic:* The observations of many investigators have established that acute exposure of normal subjects to increased CO_2 tensions may result in progressive depression of the central nervous system to the point of anesthesia. There are, furthermore, well documented observations which indicate that treatment of patients with pulmonary emphysema and CO_2 retention with high concentrations of O_2 in inspired gas may be followed by mental depression, somnolence and even coma. This sequence of events is generally ascribed to a diminution in alveolar ventilation and an increase in CO_2 retention incidental to suppression of the hypoxic stimulus. Less emphasis has been placed upon the clinical observation that the untreated patient with pulmonary emphysema and CO_2 retention is generally drowsy, apathetic and mentally sluggish. The relation of this state to chronic CO_2 retention is emphasized in the present study wherein a decrease in arterial blood P_{CO_2} and alkali reserve following prolonged diamox therapy has been shown to restore the mental alertness and vitality of these patients. Similar observations have been made by others during briefer periods of treatment with diamox.[25]

B. Methods for Prevention and Control of CO_2 Retention. Turning now to the therapeutic implications of these studies, two methods are currently available for the prevention and control of CO_2 retention, namely, the improvement of alveolar ventilation ($\dot{V}_A$), and the promotion of elimination of bicarbonate by the kidney.

1. *Improvement of alveolar ventilation* ($\dot{V}_A$): There are many ways to improve $\dot{V}_A$. These include breathing exercises, bronchodilators, reduction in pulmonary blood volume and substitution of mechanical for spontaneous regulation of ventilation.

2. *Promotion of bicarbonate excretion by the kidney:* The best method currently available is the use of carbonic anhydrase inhibitors which promote the excretion of bicarbonate and bicarbonate-bound base by the kidney, apparently by interfering with the hydrogen ion exchange mechanism for sodium.[22,23] These may also have some influence on CO_2 excretion but, although the amount of carbonic acid which may be excreted in the urine after diamox therapy is not established, it is probably insignificant. An additional effect of these inhibitors entails their role as weak diuretic agents which may indirectly augment $\dot{V}_A$ by decreasing the volume of blood in the lungs.

C. Clinical Applications of These Methods. The specific indications for the application of each of these methods depend upon the stage of the disease. From the point of view of therapy of CO_2 retention, patients with chronic pulmonary emphysema may be divided into three groups: (1) patients without CO_2 retention at rest or during activity, (2) patients with a tendency to CO_2 retention at rest or during exercise and (3) patients with chronic CO_2 retention. In all three groups acute bronchitis or pulmonary infection may precipitate or aggravate a state of respiratory acidosis. However, in the absence of acute respiratory infection the following general principles concerning the use of mechanical hyperventilators and diamox apply: (1) In the first group, mechanical hyperventilation and the use of diamox are not specifically indicated. (2) In the second group, attention should be directed toward the prevention of CO_2 retention. The use of mechanical ventilators for brief periods each day will promote the excretion of CO_2. In addition, patients addicted to O_2 therapy may find an adequate substitute in the increased alveolar O_2 tension provided by mechanical hyperventilation. The usefulness of diamox in these patients is not established. (3) In the third group, mechanical hyperventilation and diamox are indicated in an attempt to deplete CO_2 stores. In our experience with

patients of this group, previously studied over long periods of time, diamox has emerged as a valuable adjuvant to therapy. However, once initiated, its administration in one dose of 0.5 gm. per day has been continued indefinitely. Prolonged administration of diamox, with return of arterial blood P_{CO_2} and the alkali reserve toward normal, may occasionally obviate the need for mechanical hyperventilation.

Classification of a given patient according to the three groups indicated is based upon analysis of arterial blood for pH, total CO_2, P_{aCO_2} and alkali reserve, and responsiveness of the respiratory center to increase in P_{CO_2} in inspired gas. It is apparent that the most reliable guide to adequacy of any form of treatment is sequential analysis of arterial blood.

The distinction of these three groups of patients with chronic pulmonary emphysema may be obscured in acute bronchitis or bronchopneumonia which will bring about or aggravate elevation in arterial blood P_{CO_2}. However, a considerable elevation in the level of arterial blood P_{CO_2} and of alkali reserve in a patient who has not received O_2 therapy, a considerable degree of polycythemia or the presence of congestive heart failure suggest that the patient belongs to the third group of patients with chronic CO_2 retention rather than to the other two groups of patients with acute CO_2 retention. In any event the demonstration of respiratory acidosis by analysis of arterial blood demands the prompt institution of mechanical hyperventilation and diamox therapy to supplement the customary treatment with antibiotics, bronchodilators and, if need be, the specific measures for heart failure of the right side. Adequate mechanical hyperventilation is particularly essential if O_2 therapy is required to relieve severe arterial hypoxemia. It should be emphasized that occasional failure of diamox therapy is to be anticipated in patients with protracted and severe CO_2 retention and hypoxia[11d] if other therapeutic measures, particularly mechanical hyperventilation and O_2 therapy, are not instituted promptly, concomitantly and effectively. The value of diamox may be increased in the presence of congestive heart failure because of its mild diuretic action; in the patients with chronic pulmonary emphysema and CO_2 retention diamox therapy, apart from its diuretic action, facilitates clearing of the sensorium and reduces the hazard of CO_2 narcosis.

SUMMARY

1. The studies reported in this paper confirm the well documented observation that some patients with chronic pulmonary emphysema manifest an abnormally small increase in minute ventilation when CO_2 is added to inspired air. This diminished ventilatory response, despite a considerable increase in arterial P_{CO_2}, is characteristic of patients with chronic pulmonary emphysema who also have chronic CO_2 retention.

2. The mechanism underlying the abnormal ventilatory response in these patients appears to be a selective depression of the respiratory center to the stimulus of increased arterial blood P_{CO_2} and/or hydrogen ion concentration, since responsiveness to other stimuli such as exercise is well maintained. Restriction in the ventilatory capacity of the chest bellows is not the limiting factor to increase in minute ventilation during CO_2 breathing in patients with emphysema and CO_2 retention; by way of contrast, this restriction may suffice to limit the ventilatory response to the CO_2 stimulus in some patients with emphysema but without CO_2 retention.

3. The poor ventilatory response to the CO_2 stimulus is generally not reversible in patients with CO_2 retention of long duration even though the arterial blood P_{CO_2} and alkali reserve may be restored toward normal levels as a result of prolonged administration of the carbonic anhydrase inhibitor, diamox.

4. In addition to its action in decreasing the alkali reserve, diamox also reduces the arterial blood P_{CO_2}. The mechanism of this action is not established.

5. The relief or aggravation of hypoxemia within the physiologic range has little effect on the ventilatory response to inspired CO_2 in patients with emphysema and CO_2 retention. This suggests that the hypoxic stimulus is rather weak; however, as is well known, breathing pure O_2 consistently depresses the ventilatory response. The contrast between these observations emphasizes the importance of distinguishing between the physiologic and pharmacologic levels of O_2 tension in the blood.

6. The therapeutic implications of these observations, in patients with chronic pulmonary emphysema, are threefold. First, a distinction must be made between the effect of reduced ventilatory drive, and considerable restriction in ventilatory capacity in limiting minute ventila-

tion. Second, attention must be focused on the means for prevention and prompt relief of CO_2 retention. The role of diamox and of mechanical hyperventilation in the various stages of the disease has been described in this connection. Finally, by mobilizing large stores of CO_2 from the body, continuous diamox therapy in patients with prolonged CO_2 retention may restore mental alertness and a sense of well-being and diminish the threat of CO_2 narcosis.

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Pulmonary Arteriovenous Fistula*

Angiocardiographic Observations in Nine Cases

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PULMONARY arteriovenous fistulas are congenital hemangiomatous malformations of the pulmonary vascular bed. Recognition of the anomaly during life has been enhanced by the increased use of chest x-ray surveys, body section roentgenography, angiocardiography and safe exploratory thoracotomy. Sloan and Cooley[1] in 1953 reviewed eighty-five cases reported in the literature and added nine cases. In the short time since this review a total of over 150 cases[2–10] has been reported. The first clinical diagnosis of a pulmonary arteriovenous fistula was made in 1939 by Smith and Horton,[11] and the first successful surgical treatment was reported by Hepburn and Dauphiner[12] and performed by Shenstone and Janes[13] in 1942.

Pulmonary arteriovenous fistula rather than pulmonary arteriovenous aneurysm is the preferred name of the malformation and has become widely accepted. It calls to mind the characteristic features of the condition: afferent arterial and efferent venous connections. Furthermore, the term aneurysm usually refers to sac-like formations of dilated arterial vessels and does not take into account the venous component of the condition.

The diagnosis of pulmonary arteriovenous fistula formerly depended upon clinical findings such as cyanosis and clubbing of the fingers and toes, polycythemia and a murmur over a pulmonary lesion.[11–22] Later it was recognized that many patients with this clinical syndrome had associated cutaneous and mucosal hemangiomas and telangiectasis, and the hereditary nature of pulmonary arteriovenous fistulas and its relationship to Rendu-Osler-Weber's disease (hereditary capillary telangiectasis) became apparent.[16–24] Finally, with more experience came the realization that all the classical clinical features may be absent except for the roentgen findings.[23–25] Once suspicion of a pulmonary arteriovenous fistula is aroused, confirmation by fluoroscopy, laminography and angiocardiography will establish the diagnosis. It is generally agreed that angiocardiography provides the definitive diagnosis. For this reason the role that angiocardiography played in the diagnosis of nine cases of pulmonary arteriovenous fistulas (two of which were previously reported)[25] is herein reviewed.

CASE REPORTS

CASE 1. (Pulmonary arteriovenous fistula, posterior basilar segment, right lower lobe, associated with epistaxis, hemangioma of tongue and brain abscess). A thirty-nine year old housewife (New York Hosp., No. 596001) was admitted on March 22, 1950, because of right-sided convulsions and aphasia of three days' duration. There was a history of recurrent nosebleeds since childhood. On physical examination she was well developed and nourished but drowsy and aphasic with signs of right hemiplegia. A 6 mm. hemangioma was noted at the tip of the tongue. A harsh systolic murmur was heard at the base of the right lung which increased in intensity after deep inspiration. There was no clubbing or cyanosis of the fingers and toes.

Cerebral angiography and pneumoencephalography were normal but a left craniotomy disclosed a left parietal lobe abscess. The convulsions ceased but left hemiplegia and aphasia persisted. There were frequent nosebleeds during hospitalization. Chest x-rays (Fig. 1A and B) showed a heart of normal size and a rounded mass at the right base which had afferent and efferent vascular connections. Angiocardiography (Fig. 1C) confirmed the presence of an

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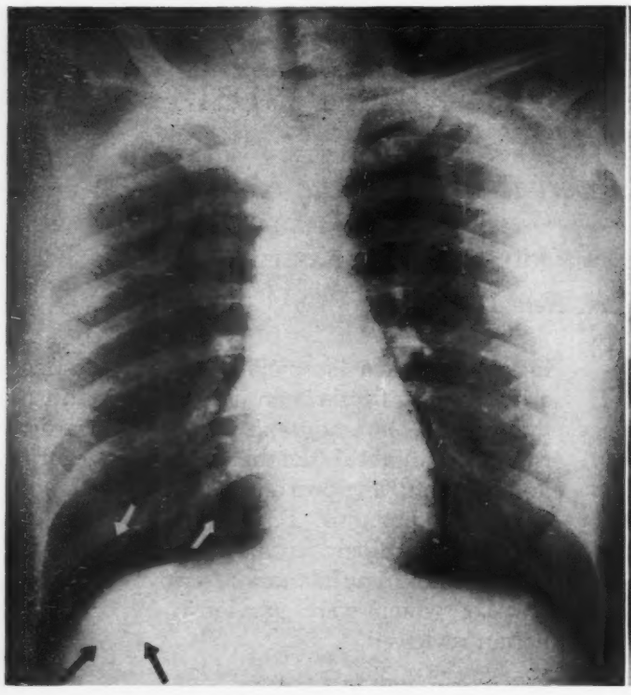

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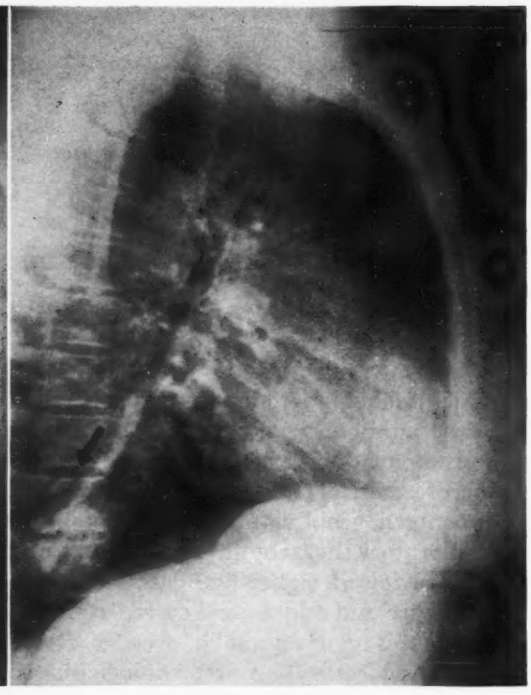

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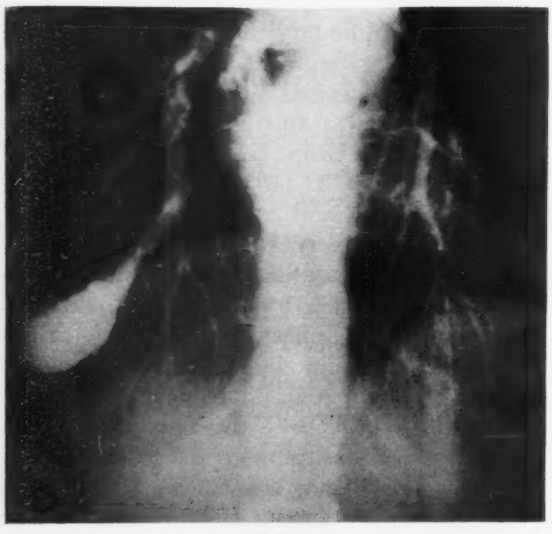


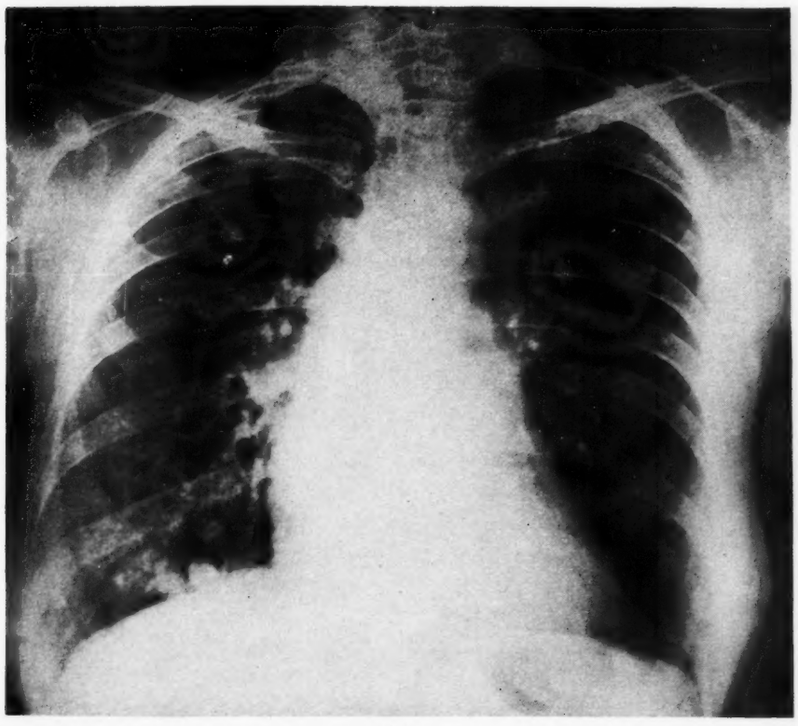
1C

FIG. 1. Case I. Pulmonary arteriovenous fistula, posterior basilar segment, right lower lobe complicated by brain abscess. A, conventional frontal roentgenogram showing a large single rounded density behind right diaphragm (arrows). Afferent (arrow) pulmonary arterial branch and efferent (arrow) venous communication readily discerned. B, right lateral conventional roentgenogram clearly reveals pulmonary arteriovenous fistula with characteristic afferent (arrow) and efferent communications. C, frontal serial angiocardiogram at four seconds after the beginning of injection shows the opacified arteriovenous fistula with its efferent communication proceeding towards the left hilum.

arteriovenous fistula in the posterior basilar segment of the right lower lobe.

The electrocardiogram was normal. On a return visit, July 22, 1954, examination disclosed persistence of the hemiplegia and aphasia but the patient was able to take care of her household chores. Her poor general condition precluded resection of the pulmonary arteriovenous fistula. Table I summarizes the findings.

CASE II. (Pulmonary arteriovenous fistula, medial basilar segment, right lower lobe, associated with rheumatic heart disease and hypertension.) A sixty-five year old housewife (New York Hosp., No. 319819) was first admitted in 1946 because of blurred vision. A middle fossa meningioma was found, and removal of the tumor resulted in improvement of vision. During her stay evidences of mitral stenosis and insufficiency were elicited. In 1947 she returned because of epigastric cramps. Urologic study at that time disclosed cysts of the right kidney, which were removed. Chest x-ray (Fig. 2A)



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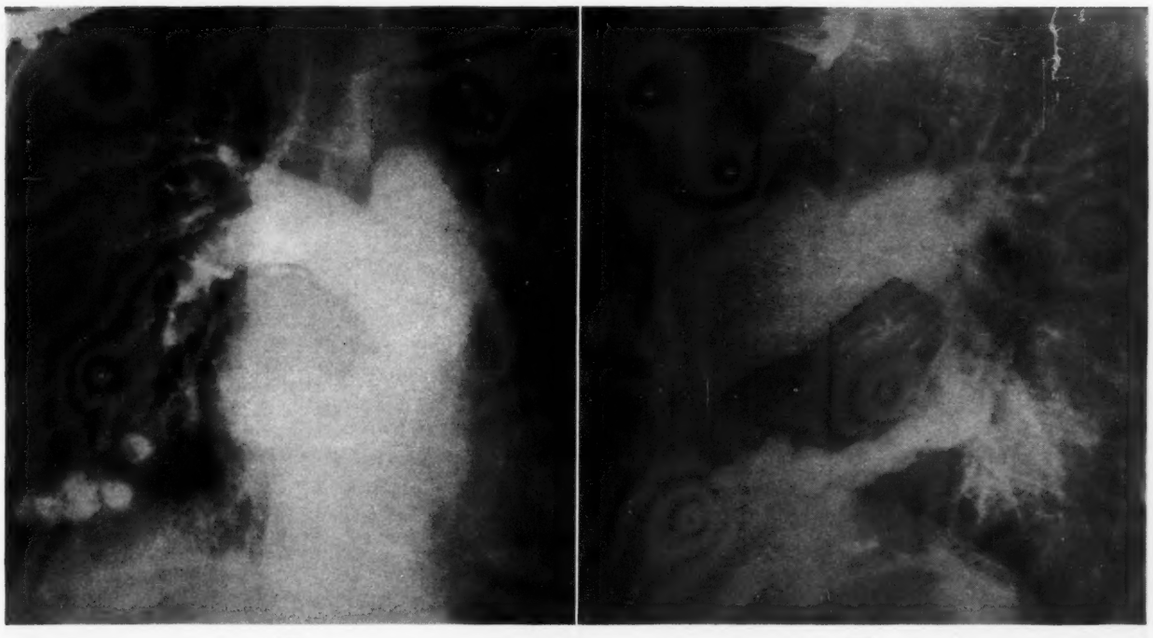

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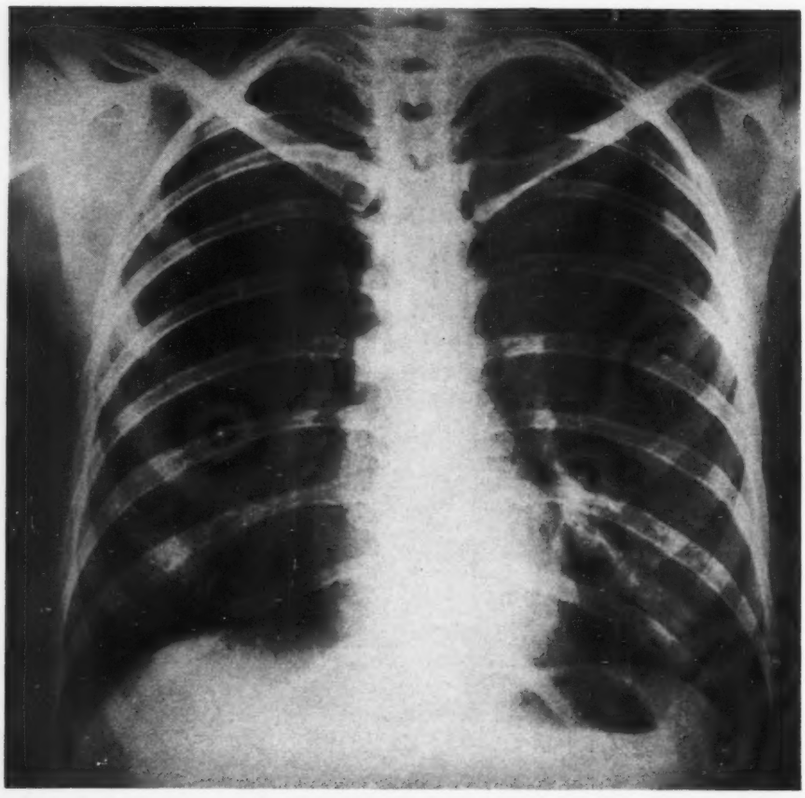
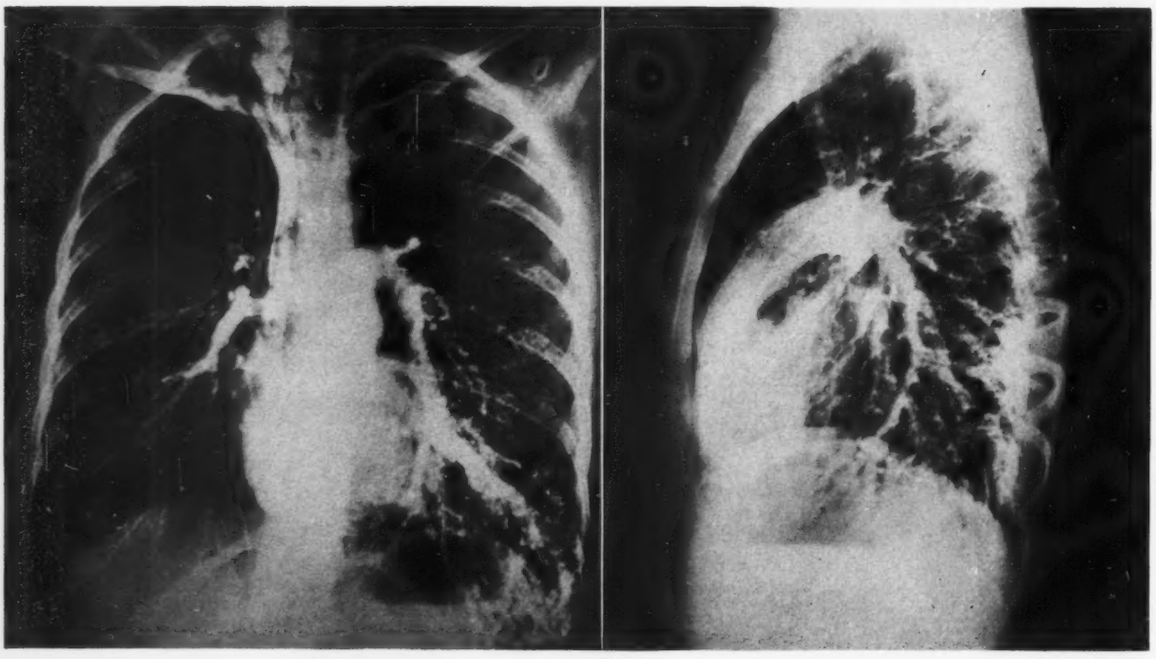
FIG. 2. Case II. Pulmonary arteriovenous fistula, medial basilar segment, right lower lobe in a patient with rheumatic heart disease (mitral stenosis). A, conventional frontal roentgenogram showing a nest of small nodular densities just above the right diaphragm. The heart, pulmonary artery and branches are enlarged. B, serial frontal angiocardiogram at five seconds shows a large pulmonary artery and branches. A large segmental pulmonary artery from the right descending branch of the pulmonary artery proceeds to the right lower lobe connecting with a coiled series of rounded densities (arteriovenous fistula) which in turn empty via an efferent vessel into the left atrium. C, left lateral angiocardiogram at three seconds shows the opacified main stem pulmonary artery and branches with an afferent basilar segmental division connecting the circinate arteriovenous fistula.

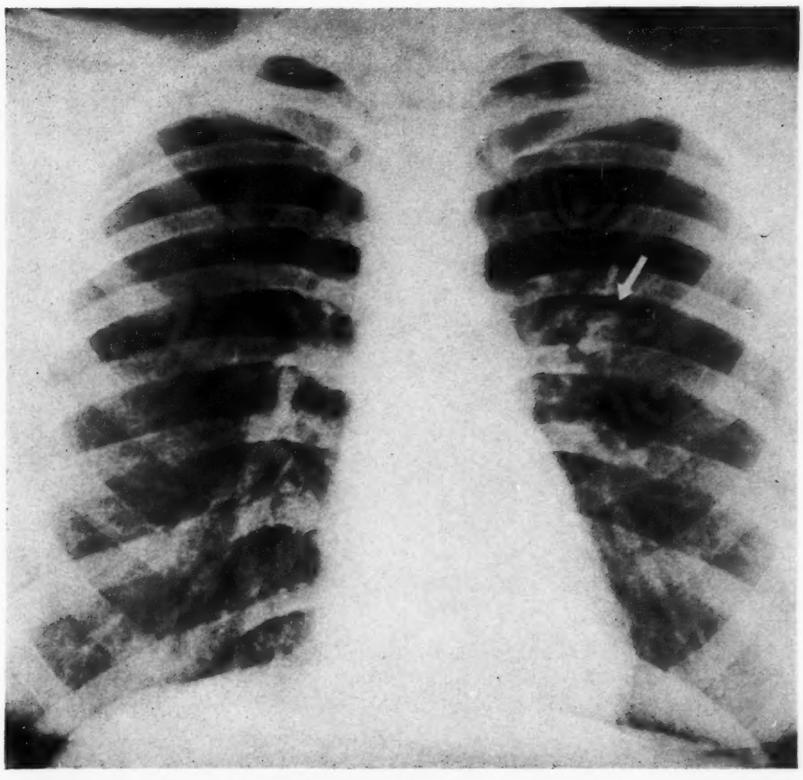


3A



3B 3C

FIG. 3. Case III. Left lower lobe arteriovenous fistula in a thirty-one year old woman with cyanosis, polycythemia and clubbed fingers. A, conventional frontal roentgenogram showing linear hazy infiltrate-like density at left base. B, frontal angiocardiogram at two and one-half seconds showing the arteriovenous fistula. C, left lateral angiocardiogram at two and one-half seconds again demonstrating the left lobar arteriovenous fistula.[54]



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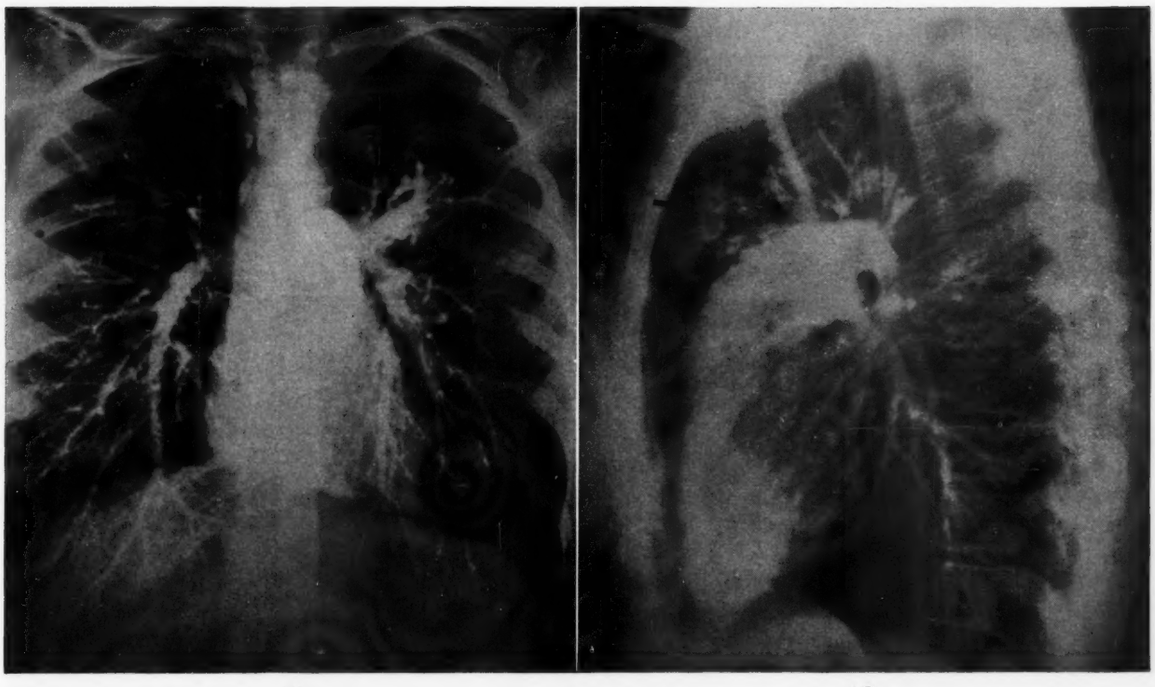
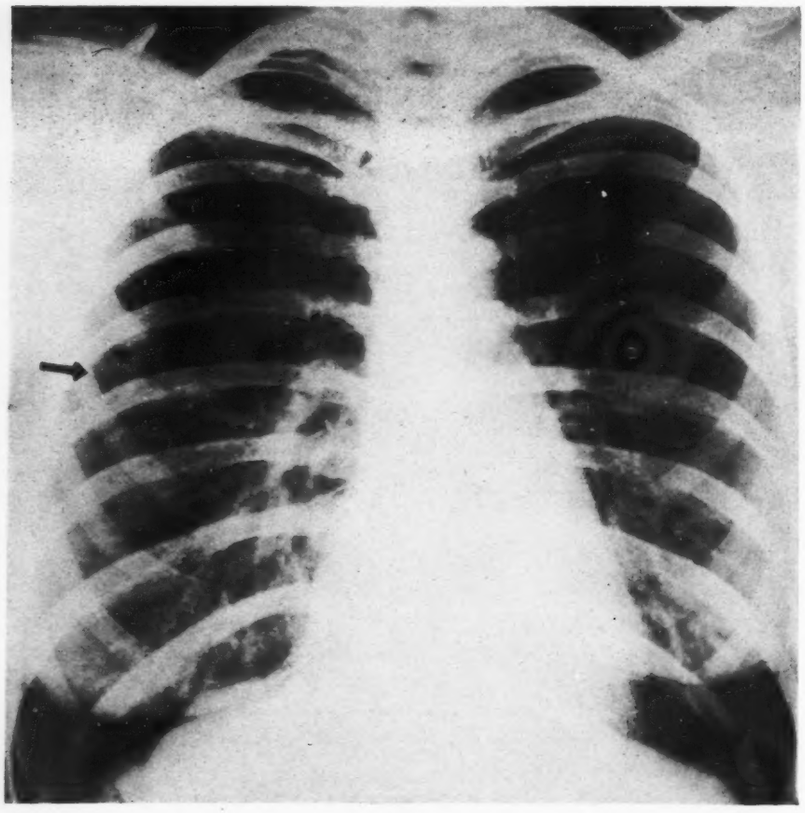


4B 4C

FIG. 4. Case IV. Anterior segment left upper lobe arteriovenous fistula in an asymptomatic sibling. A, conventional frontal roentgenogram reveals an "infiltrate" (arrow) left hilar region. B, frontal angiocardiogram at two and one-half seconds shows the arteriovenous fistula (arrow). C, left lateral angiocardiogram at two and one-half seconds localizes the arteriovenous fistula (arrow) in the anterior segment of the left upper lobe.[25]



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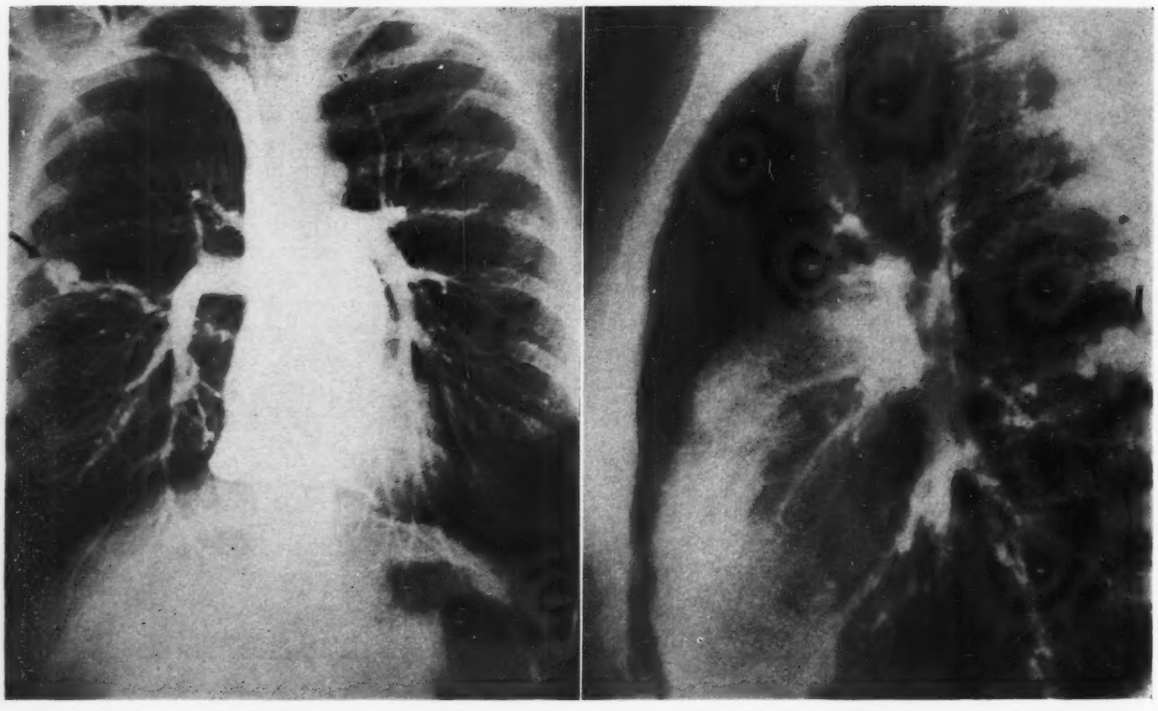


5B 5C

FIG. 5. Case v. Apical segment right lower lobe arteriovenous fistula in an asymptomatic sibling. A, frontal conventional roentgenogram reveals two tiny rounded densities (arrow) in outer portion right mid-lung field. B, frontal angiocardiogram at two and one-half seconds reveals the arteriovenous fistula with its opacified vascular connections. C, left lateral serial angiocardiogram shows the fistula in the apical segment of the right lower lobe.

revealed nodular densities at the right base. The heart was enlarged, especially the right ventricle, pulmonary artery segment and left atrium. The blood pressure in 1946 was normal but in 1947 it had increased to 220/110.

In 1949 cholelithiasis with obstructive jaundice developed which necessitated cholecystectomy and choledocholithotomy. Auricular flutter appeared prior to operation and was converted by digitalization to fibrillation. The postoperative period was stormy but the patient improved and was discharged. Subsequently she was seen periodically in the out-patient department. Early in 1951 central retinal artery thrombosis developed and she was readmitted to the hospital. This time the findings at the right base were suspected to be due to pulmonary arteriovenous fistula; however, no bruit was heard and clubbing and cyanosis of fingers and toes were not present. Angiocardiography (Fig. 2B and C) was performed and an arteriovenous fistula of the anterior basilar segment of the right lower lobe was demonstrated.

The electrocardiogram showed right axis deviation; the rhythm varied between auricular flutter and fibrillation. The patient was last seen on June 24, 1954. She was totally blind, but polycythemia, clubbing and cyanosis of the fingers had not developed. Because of her poor general health and the asymptomatic character of the pulmonary arteriovenous fistula, operation was not advised. (Table I.)

Case III. (Pulmonary arteriovenous fistula of the left lower lobe associated with polycythemia, cyanosis and clubbing of fingers and toes.) A thirty-one year old housewife (New York Hosp., No. 322967) had a routine prenatal chest film (Fig. 3A) at a New York City Health Department Chest Clinic, which disclosed an abnormal shadow at the left base. Following delivery dyspnea developed, and clubbing and cyanosis of the fingers and toes were noted. A bronchogram showed no evidence of bronchiectasis. Subsequently a vascular bruit was heard at the left base and the patient was referred for angiocardiography. On angiocardiography a left lower lobe arteriovenous fistula was demonstrated (Fig. 3B and C) and she entered the hospital for operation.

On admission April 19, 1950, the patient was found to be well developed but poorly nourished and chronically ill. Her heart was not enlarged; a blowing systolic murmur was heard at the pulmonic area. In the lower posterior

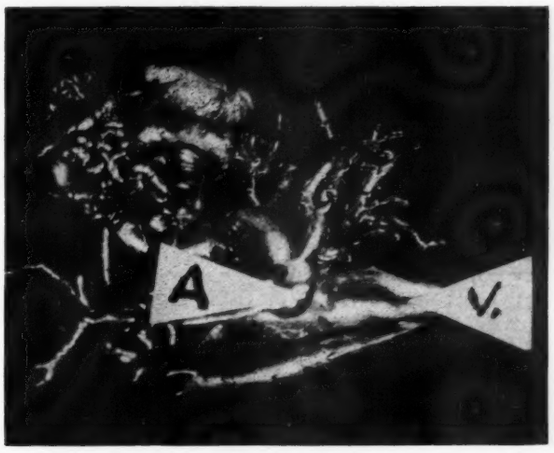


Fig. 5D. Case v. Apical segment right lower lobe arteriovenous fistula in an asymptomatic sibling; low melting alloy cast of specimen, A, afferent artery and V, efferent vein.[25]

area of the left lung, in the mid-axillary line, a loud bruit with systolic and diastolic components was heard. The murmur decreased after deep inspiration and disappeared after the Valsalva maneuver. The blood pressure was 105/75.

An electrocardiogram showed normal sinus rhythm at a rate of 72 per minute and no deviation of the electrical axis. Fluoroscopic examination failed to reveal vascular pulsations at the left base, or change in size of the left lower vascular tree with respiratory movements. Operation was advised but refused; the patient went home and has not returned for follow-up examination. (Table I.)

Case IV. (Asymptomatic pulmonary arteriovenous fistula, anterior segment, left upper lobe, in a sibling treated with lobectomy.) A nineteen year old typist (New York Hosp., No. 573907), previously reported on,[25] was found to have a pulmonary infiltrate (Fig. 4A) in 1950 when she applied for working papers. Because of a negative tuberculin test she was referred by a New York City Department of Health Tuberculosis Clinic for angiocardiography. This revealed (Fig. 4B and C) an arteriovenous fistula of the anterior segment of the left upper lobe. The patient was well developed and nourished, asymptomatic, and presented no abnormal physical findings. Subsequently a faint vascular bruit was heard, especially after deep inspiration, over the third left anterior interspace. A left upper lobectomy was performed and the patient made an uneventful recovery. (Table I.)

Case V. (Asymptomatic pulmonary arterio-

venous fistula, apical segment, right lower lobe, in a sibling treated with segmental resection.) A twenty-two year old housewife (New York Hosp., No. 616053), previously reported on,[25] had been aware of a right lung infiltrate following a chest x-ray survey at the age of fourteen years.

TABLE I

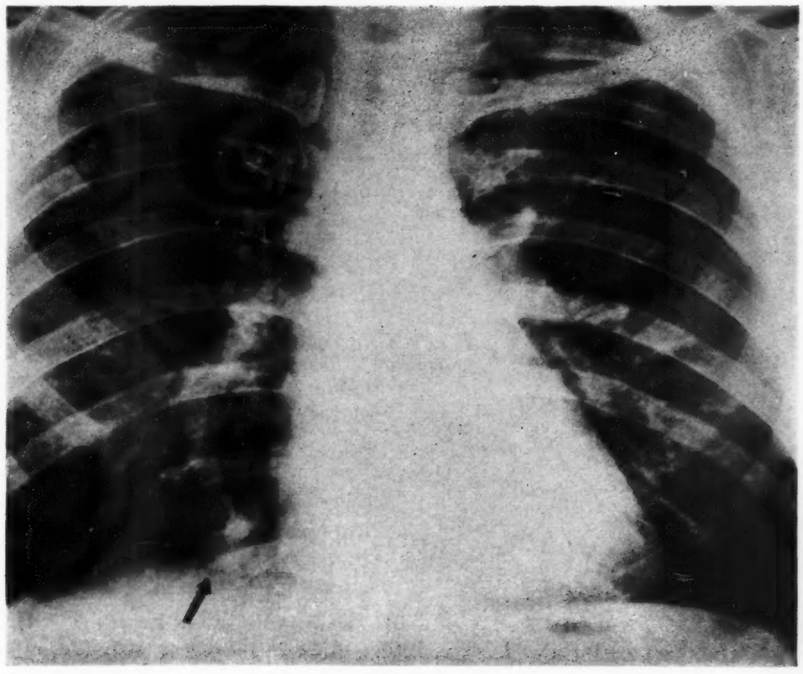
SUMMARY OF FINDINGS IN EIGHT CASES OF PULMONARY ARTERIOVENOUS FISTULAS

Case, Age, Sex	Lung	Lobe or Segment	Associated Conditions	Bruit	Hemoglobin (gm./100 cc.)	Red Blood Count (m./cu./mm.)	Hematocrit (%)	Comment, Operation and Follow-up
I, 39, F	R	Posterior basilar segment, right lower lobe	Epistaxis, hemangioma of tongue; left parietal lobe brain abscess	+	11.6 to 13.5	5.2	..	Convulsions ceased after drainage of brain abscess; hemiplegia persists; 4 yr. follow-up shows no change in cerebral or chest conditions; poor general condition precluded excision of fistula
II, 67, F	R	Medial segment, right lower lobe	Rheumatic heart disease and hypertension	0	13.5 to 16.4	4.7 to 5.6	..	During 4 yr. follow-up patient has had 3 operations (excision of meningioma, nephrectomy and cholecystectomy); auricular flutter and fibrillation and central retinal artery thrombosis occurred but lung lesion remains unchanged; operation of lung lesion not advised
III, 31, F	L	Left lower lobe	Dyspnea, polycythemia, cyanosis, clubbing of fingers	+	18.8	5.7	57	Operation refused; no follow-up
IV, 19, F	L	Anterior segment, left upper lobe	Asymptomatic	+	13.5	5.4	44	Sibling, remains asymptomatic after left upper lobectomy
V, 22, F	R	Apical segment, right lower lobe	Asymptomatic	+	14.5	4.1	42	Sibling, remains asymptomatic after segmental resection
VI, 54, M	R	Posterior basilar segment, right lower lobe	Subacute thyroiditis	+	14	4.7	48	Right lower lobectomy because of bronchial arterial connection of fistula; uneventful recovery ensued
VII, 31, M	R	Right middle lobe	Acute meningoencephalitis	+	15.6	4.9	..	Complete recovery from meningoencephalitis after 4 mo. antibiotic and chemotherapy; lobectomy, right middle lobe, no complications
VIII, 36, M	L	Lingular segment, left upper lobe	Asymptomatic	+	17	5.7	..	Abnormal shadow left lung discovered on routine chest film; lingulectomy and uneventful recovery
IX, 50, F	R L	Superior segment, right upper lobe Posterior basal segment, left lower lobe	Dyspnea, weakness, epistaxis, familial telangiectasis, cyanosis of finger tips	+ +	9.9	4.0	35	In spite of classical symptoms and signs of Rendu-Osler-Weber's disease and associated pulmonary arteriovenous fistulas, diagnosis only recently made; lobectomy left lower lobe; excision of fistula, posterior segment, right upper lobe planned

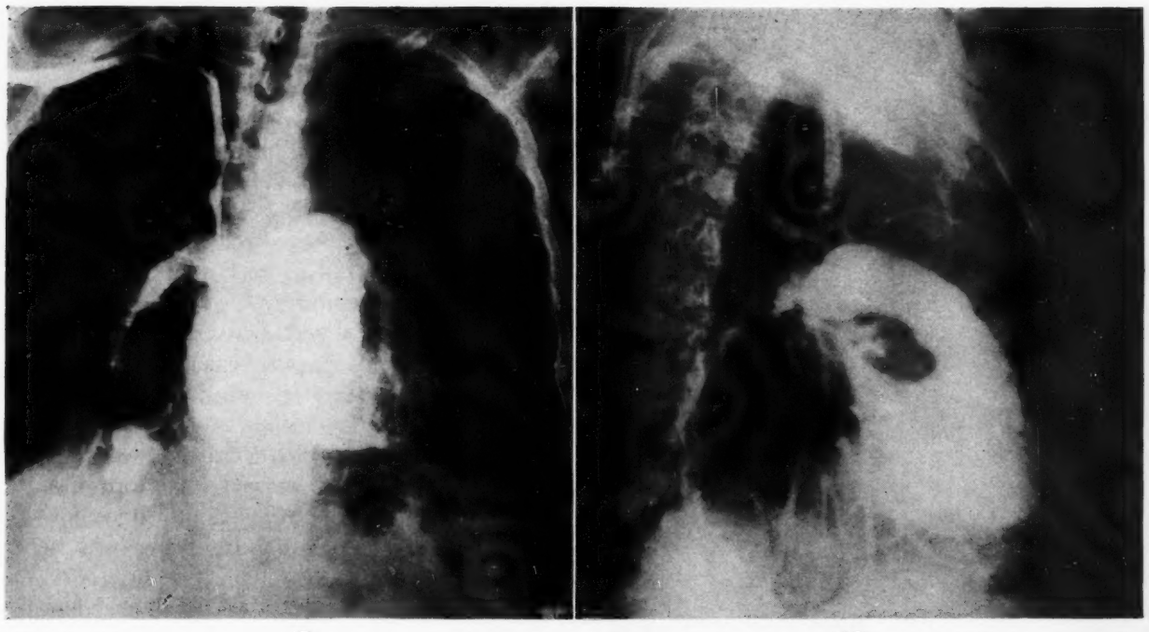
(Fig. 5A.) Following the finding of a pulmonary arteriovenous fistula in her sister (Case IV) she had an angiocardiographic study (Fig. 5B and C) which disclosed an arteriovenous fistula of the apical segment of the right lower lobe. She was asymptomatic. Physical examination revealed only a faint systolic murmur at the sixth interspace in the right mid-axilla.

On January 22, 1953, segmental resection of the apical segment of the right lower lobe was performed. The patient made an uneventful recovery. (Table I.) A low-melting alloy cast of the excised specimen (Fig. 5D) showed the single afferent artery (*A*) to be rather straight, slightly dilated and the source of a normal number of arterioles. It abruptly entered, through three branches, a single tortuous cluster of saccules almost 2 cm. in diameter which was drained by a single dilated vein (*V*) soon joined by another vein from adjacent lung.

CASE VI. (Asymptomatic pulmonary arteriovenous fistula, posterior basilar segment, right lower lobe, treated with lobectomy.) A fifty-four year old sales manager (New York Hosp.,



6A



6B 6C

FIG. 6. Case VI. Posterior basilar segment arteriovenous fistula of right lower lobe in a patient with subacute thyroiditis. A, conventional frontal roentgenogram reveals a rounded density above the right diaphragm (arrow). B, frontal angiocardiogram clearly shows the arteriovenous fistula with its afferent arterial and efferent venous connections. C, right anterior oblique angiocardiogram localizes the arteriovenous fistula in the right posterior basilar segment of the right lower lobe.

FIG. 6D. Case VI. Posterior basilar segment arteriovenous fistula of right lower lobe in a patient with subacute thyroiditis; low melting alloy cast of the fistula.

No. 678872) was admitted because of thyroid swelling which was diagnosed as subacute thyroiditis (Quervain's disease). A routine chest x-ray (Fig. 6A) disclosed a rounded nodular parenchymal shadow at the right base, closely related to the descending branches of the right pulmonary artery. At the lower pole of the lesion an efferent branch proceeding toward the right hilus was seen. Prior to admission this area had been interpreted as being due to pulmonary metastases or a hamartoma.

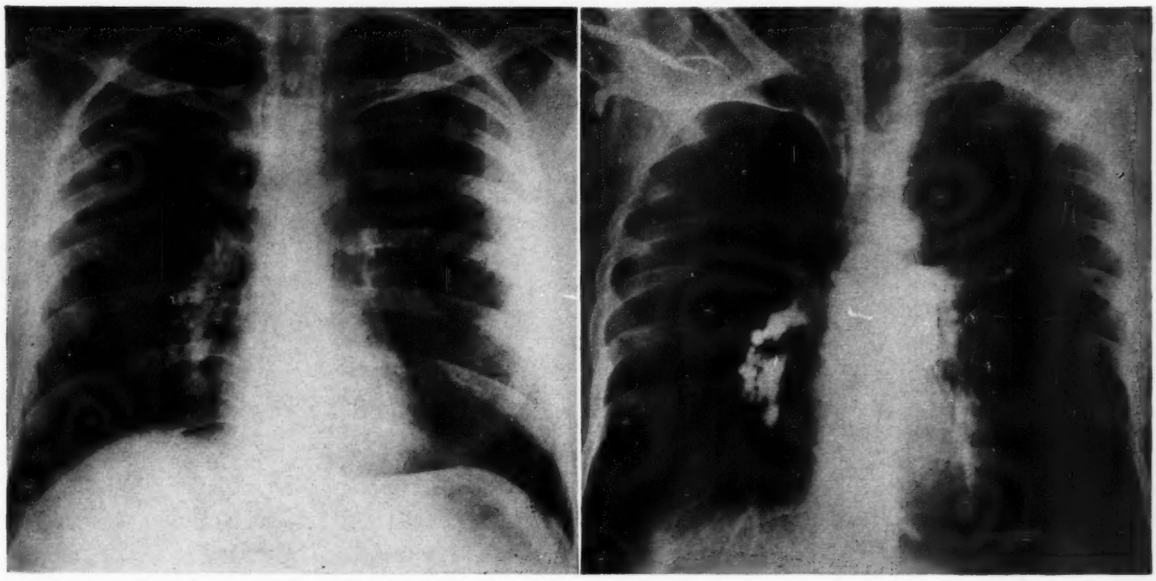
Angiocardiography (Fig. 6B and C) clearly established the presence of a pulmonary arteriovenous fistula of the posterior basilar segment of the right lower lobe. Previously, a vascular bruit was heard at the right base. Cyanosis and clubbing of the fingers and toes were not present. The heart was normal; the blood pressure was 130/80; the electrocardiogram was also normal.

At operation on May 26, 1954, three large lower lobe pulmonary vessels were seen. A ligature placed around the largest (middle branch) failed to collapse the pulsating arteriovenous fistula. Only after ligation and division of the pulmonary arteries and the bronchus of the lower lobe with its bronchial arterial blood supply (lobectomy) did pulsation of the fistula cease. The patient made an uneventful recovery. (Table I.)

The excised fistula was injected with low melting alloy with some difficulty as its main afferent vessel was found only after a long search. (Fig. 6D.) The artery followed a long, gently curved course to the posterior basal segment and then proceeded by a single branch into an extremely thin-walled sac with filmy septations. A single dilated vein drained the sinus.

CASE VII. (Pulmonary arteriovenous fistula, right middle lobe, treated with lobectomy; complicated by acute meningoencephalitis.) A thirty-one year old laborer (New York Hosp., No. 682240) was referred for angiocardiography from the Brooklyn Veterans Administration Hospital. The patient became acutely ill in November, 1953, with bitemporal headaches, episodes of unconsciousness, olfactory hallucinations and generalized convulsions. Fever, a generalized maculopapular rash, nuchal rigidity, hyperflexia, increase in spinal fluid cells and proteins with a diminished sugar content were present. Spinal and blood cultures were sterile. Complete recovery occurred after four months of intensive treatment with antibiotics and chemotherapy. The final diagnosis was acute meningoencephalitis.

While the patient was at the Veterans Hospital a grade II systolic murmur was heard over the right anterior chest at the fourth anterior interspace near the sternum. The electrocardiogram was normal. Chest roentgenogram (Fig. 7A) disclosed increased vascularity in the right hilus which on lateral view was located in the middle lobe. Angiocardiography



7A 7B

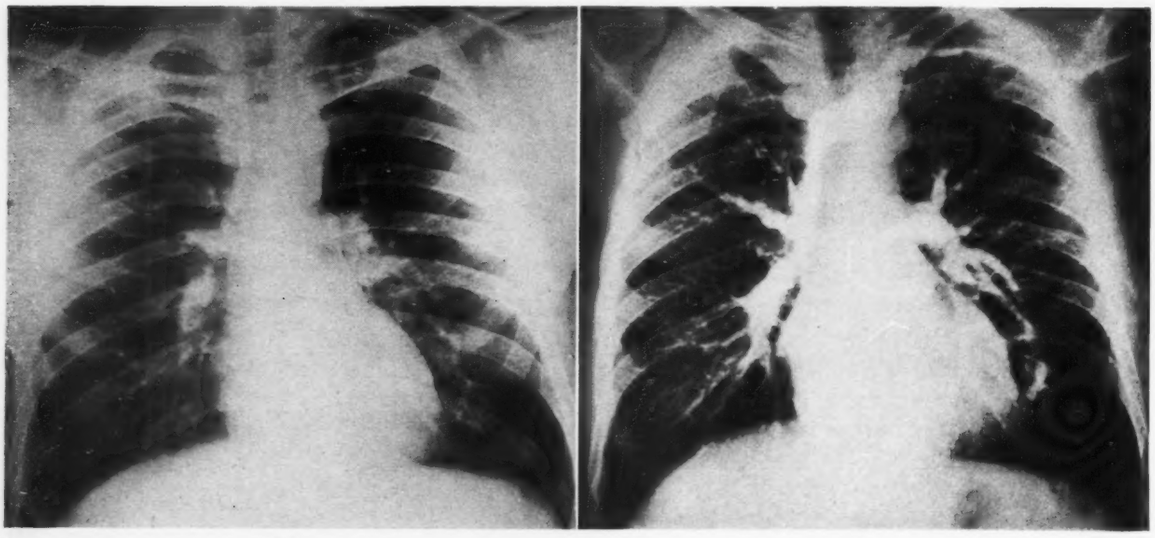
FIG. 7. Case VII. Right middle lobe arteriovenous fistula in a patient with meningoencephalitis. A, conventional frontal roentgenogram shows increased vascularity of right hilar vessels. B, frontal angiocardiogram shows arteriovenous fistulous malformation. Lateral view (not shown) showed fistula to be in middle lobe.

(Fig. 7B) established the diagnosis of arteriovenous fistula of the right middle lobe. On May 11, 1954, a right middle lobectomy was performed at the Brooklyn Veterans Administration Hospital and the patient made an uneventful recovery. (Table I.)

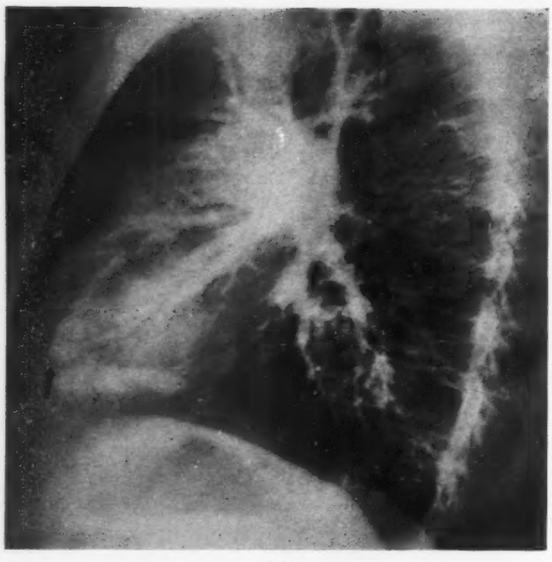
A low-melting alloy cast of the fistula showed it to occupy most of the medial segment of the right middle lobe. It consisted of a rather stubby, wide pulmonary artery branching into a plexus of intermeshed thin vessels converging into a single dilated vein approximately 1.0 cm. in diameter which also ran, without tributaries, to the right hilus. (Fig. 7C.)

CASE VIII. (Asymptomatic pulmonary arteriovenous fistula, lingular segment, left upper lobe.) On routine chest x-ray (Fig. 8A) a thirty-six year old male schoolteacher (New York Hosp., No. 672688) was found to have increased vascularity along the route of the left descending pulmonary arterial tree. The patient was asymptomatic. On examination he was in good general condition. The heart was normal in size; there were no murmurs; the blood pressure was 120/80; and there was no cyanosis. A bruit was heard after deep inspiration just to the left of the apex of the heart. The arterial oxyhemoglobin was 94 per cent saturated at rest, and the shunt through the pulmonary arteriovenous fistula was calculated to be 15 to 18 per cent of the total pulmonary blood flow.

FIG. 7C. Case VII. Right middle lobe arteriovenous fistula in a patient with meningoencephalitis; low melting alloy cast of lesion.



8A 8B



8C

FIG. 8. Case VIII. Lingular segment (left upper lobe) arteriovenous fistula in an asymptomatic male. A, frontal roentgenogram shows increase in vascularity left lower lung field. B, frontal angiocardiogram shows a small arteriovenous fistula. C, lateral angiocardiogram reveals the arteriovenous fistula (arrow) segment with its afferent and efferent branches in the lingular.

Angiocardiography (Fig. 8B and C) revealed a pulmonary arteriovenous fistula in the lingular segment of the left lung. On February 4, 1955, the lingular segment was excised and the patient made an uneventful recovery.

CASE IX. (Pulmonary arteriovenous fistulas, posterior segment right upper lobe and posterior basal segment left lower lobe, associated with Rendu-Osler-Weber's disease.) A fifty year old housewife (New York Hosp., No. 702800) was admitted on February 10, 1955, with complaints of dyspnea and tiredness of ten years' duration. For over twenty years she had been aware of "red spots" on the lips and fingers. As a child she had had frequent nosebleeds; these gradually decreased, recurring only two to three times a year. She had always considered herself well. Six pregnancies were uncomplicated, but during her seventh in 1939 fatigue and dyspnea on exertion began. Anemia was discovered and a "tonic" containing iron was prescribed. She improved and was even able to manage work in a factory. However, two or three times each year she had excessive fatigue, dyspnea and headache which required an iron "tonic" and a month's leave of absence from her job.

In 1949 a routine survey chest x-ray disclosed pulmonary lesions and she was hospitalized for six weeks in a tuberculosis sanatorium. On discharge she was told that she did not have

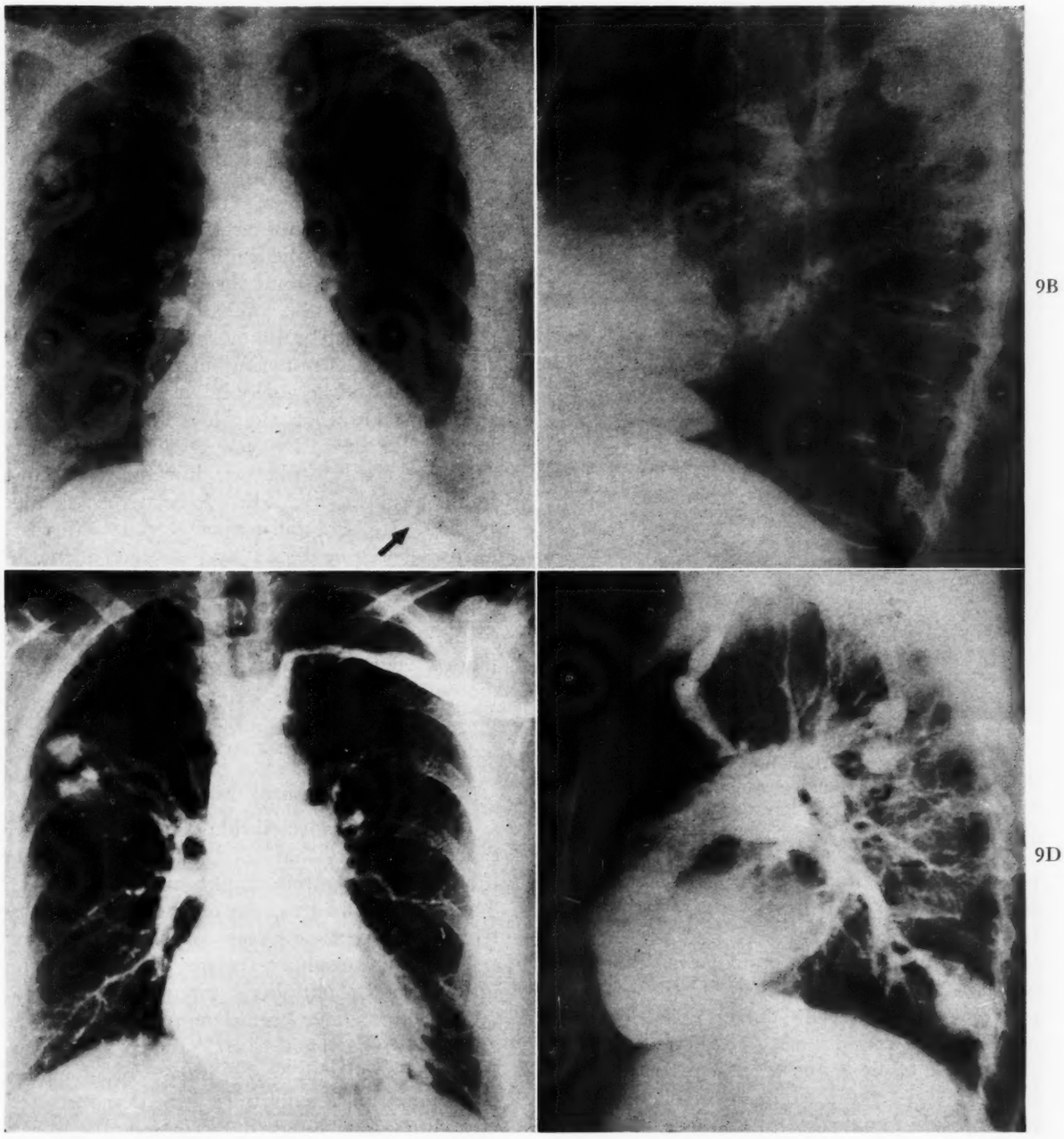


FIG. 9. Case IX. Pulmonary arteriovenous fistulas of the posterior segment right upper lobe and posterior basilar segment of the left lower lobe. A, conventional frontal x-ray shows two rounded opacities in the right upper lobe with hilar connecting afferent and efferent blood vessels. Left lower lobe lesion obscured by heart and diaphragm (arrow). B, lateral, shows the posterior location of the upper lobe densities and another large rounded mass at the base. C, frontal angiocardiogram demonstrates the bilateral pulmonary arteriovenous fistulas. D, lateral angiocardiogram reveals the segmental and posterior location of the fistulas.

tuberculosis; no other diagnosis was made. Fatigue and dyspnea continued and became worse four years before the present admission, requiring a six-month period of rest before she could resume her household duties. A severe upper respiratory infection caused her to be hospitalized recently. A new chest x-ray was made, and this time a physician heard bruits and recognized the presence of bilateral pulmonary arteriovenous fistulas and familial telangiectasis. She was referred to this hospital for treatment. The patient recalled that her

FIG. 9E. Case IX. Pulmonary arteriovenous fistulas of the posterior segment right upper lobe and posterior basilar segment of the left lower lobe; low melting point alloy cast of the left lower lobe fistula.

father and two paternal uncles had "red spots" on the fingers and lips; four siblings and six children are, she believes, free of stigmas of telangiectasis.

On examination the patient was pale, and well developed and nourished. There was slight cyanosis of the lips and finger nails. The skin and mucous membranes showed multiple telangiectasis of lips, buccal mucous membrane, palate, nasal septum, right lower eyelid, finger tips and subungual regions, and toes. There was no clubbing. The heart was normal in size and there were no murmurs; blood pressure was 130/70. The electrocardiogram was normal.

Vascular bruits were heard at the base of the left lung and over the right posterior upper chest. Roentgenograms of the chest (Fig. 9A and B) showed two discrete rounded homogeneous lesions in the posterior segment of the right upper lobe with vascular connections to the hilar structures. The lateral film (Fig. 9B), in addition, revealed a larger rounded dense mass at the base, hidden from view in the frontal projection by the left diaphragm. Angiocardiography in frontal and lateral views (Fig. 9C and D) showed the fistulas. Gastrointestinal and colonic x-ray examinations and proctoscopy failed to reveal gastrointestinal telangiectasis; the stools were free of blood.

Laboratory data (Table 1) showed secondary anemia. The arterial oxygen content in volumes per cent was 14.4, the arterial oxygen capacity 16.5 per cent, and the arterial oxygen saturation 97 per cent. The shunt through the pulmonary arteriovenous fistulas was calculated to be 24 per cent of the total pulmonary blood flow. After three 250 cc. transfusions of packed cells, the hematocrit and hemoglobin were increased. On February 11, 1955, left lobectomy was performed. Postoperative recovery was uneventful.

The excised fistula was injected with low-melting alloy. (Fig. 9E.) A relatively slender branch of the pulmonary artery (arrow) abruptly became dilated and assumed a sinuous course as it entered an ovoid cluster of extremely thin-walled vessels 2.5 cm. in diameter. The fistula was drained by a single tortuous, distended efferent vein approximately 6 mm. in diameter.

DISCUSSION

Pathologic Features

It was long suspected that channels of greater diameter than that of capillaries connect branches of the pulmonary artery and vein. The evidence for this rests on the fact that relatively large particles, such as clumps of tumor cells and Schistosoma cercariae, pass through the lungs into the peripheral circulation. Arteriovenous shunts have been demonstrated in lower animals by Clark and Clark[26] and in the human stomach[27] and skin.[28] By means of ingenious perfusion experiments they were demonstrated in mammalian lungs by Prinzmetal and his group,[29] and their distribution in human lungs was charted by Tobin and Zariquiey.[30] The possible implications of these studies are the subject of a critical report by Brink.[31]

For unknown causes, chiefly congenital, arteriovenous anastomoses and capillaries become engorged and congested, and may do so in any number of patterns. The lesions are usually multiple and may vary in appearance from simple or cirsoid aneurysms of the face, neck or extremities[32] to the more extensive hemorrhagic telangiectasis of Rendu-Osler-Weber's disease.

Capillary or cavernous arteriovenous aneurysms of the viscera, frequently of the lungs, are but two kindred forms of a versatile disease. The multiplicity of the anomalies is important: In their survey of the eighty-five recorded cases of congenital pulmonary arteriovenous fistulas Sloan and Cooley[1] reported two or more lobes to be involved in twenty-seven patients, and both lungs in twenty-one. Figure 9 illustrates a case in which there were arteriovenous fistulas in the right and left lungs.

The gross appearance of the six resected fistulas in our series was in no way unusual. All were thin, globular sacs lying peripherally just beneath the pleura, supported by a rather frail stroma. In none of our specimens were calcified plaques found.

The blood supply and drainage of congenital arteriovenous fistulas is capricious and of the greatest importance at the time of thoracotomy. The varied possibilities are indicated in Figures 5D, 6D, 7C and 10. Clearly, the fistula is not simply a distended sac fed by an end artery and drained by a vein, but rather one part of an intricate anomaly affecting not only the principally involved lung but also neighboring vessels, chest wall and often the opposite lung as well. Communications may exist between terminal arteriole and vein;[33] but the artery and vein often follow an unconventional course. The artery may emerge from a normal adjacent lobe,[34] from the aorta[35] or from intercostal arteries.[6] Veins from normal adjacent lung may flow into the aneurysmal sac,[36] and wholly bizarre vessels may drain the fistula. It has been suggested, as in our Case VI, that bronchial arteries may contribute to the fistula[37] and a parallel series of direct shunts may connect the pulmonary artery and vein.[1] (Fig. 10.)

A limited amount of information about vascular lesions may be obtained by injecting them with radiopaque solutions such as barium, bismuth oxychloride,[38] cinnabar[39] or latex[40] and then making radiographs of the specimen before sectioning it. In this way the tissue may be examined histologically if the pathologist so desires. Yet the gross anatomy of these lesions and its continuity offers more information than microscopic examination, and the injection-corrosion method best demonstrates the origin, size and relationship of the vessels making up the fistula. Four of our six specimens were reconstructed by injecting them with a metal alloy of low melting point[41] and digesting the surrounding tissue with a strong alkali. It would perhaps have been as easy to inject vinylite plastic, as suggested by Liebow,[42] a method offering the additional advantage of color identification to a three-dimensional cast.

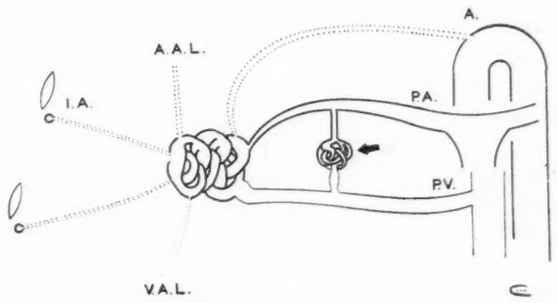


FIG. 10. Schematic drawing of anomalous connections of a pulmonary arteriovenous fistula. Continuous lines represent the pulmonary artery (P.A.) entering and the dilated branch of the pulmonary vein (P.V.) leaving the fistula. Dotted lines indicate anomalous branches from the aorta (A), the artery from the adjacent lobe (A.A.L.), vein from adjacent lobe (V.A.L.) and intercostal artery (I.A.). Small collateral shunts (arrow) may also be present proximal to the fistula, connecting pulmonary artery and vein as indicated above.

Clinical Features

Incidence, Sex and Race. Pulmonary arteriovenous fistulas are uncommon despite the increasing reports in the literature. In this Center only nine cases were collected in a total of 2,000 patients studied angiocardiographically during an eight-year period. The nine cases represent a select group: Two (Cases VII and VIII) were referred for more complete angiocardiographic study after the diagnosis had been established by angiocardiography elsewhere; two others (Cases III and IV) were referred from the Tuberculosis Clinics of the New York City Department of Health. Only five cases were found in The New York Hospital (Cases I, II, V, VI and IX) during the years 1950–1955. As in Sloan and Cooley's report,[1] there was no significant sex preference; six patients were female and three were male. The ages varied between nineteen and sixty-seven years and all patients were of the white race.

Familial Tendency and Relation of Pulmonary Arteriovenous Fistulas and Hereditary Hemorrhagic Telangiectasis. Two siblings (Cases IV and V) were among the eight cases. (Table I.) This is the third set of siblings reported in the literature.[16,18] Pulmonary arteriovenous fistulas in father and son,[43] in daughter and probably father,[1]

and mother and son[10] have also been reported recently. A history of hemangiomas and telangiectasis (Rendu-Osler-Weber's disease) in other members of the family in our eight patients could only be elicited once (Case IX). In the literature, however, 15 per cent had a familial history of this disease.[1] Two of the patients (Cases I and IX) had associated hemangiomas, and over 40 per cent of the reported cases of pulmonary arteriovenous fistula also had telangiectatic lesions elsewhere in the body.[1] These findings clearly establish the familial nature of pulmonary arteriovenous fistula and the close relation to hereditary hemorrhagic telangiectasis.

Symptoms and Physical Findings. Only one patient (Case III, Table I) had dyspnea, cyanosis and clubbing of the fingers and toes. The findings were due to anoxemia and resulted from involvement of the whole left lower lobe (the largest in our series) in the arteriovenous fistula. (Fig. 3.) This is in contrast to the forty-four instances of dyspnea among the seventy-nine cases collected from the literature by Sloan and Cooley,[1] and suggests that only the large and more advanced pulmonary arteriovenous fistulas have hitherto been recognized. The absence of cyanosis and polycythemia in Case VI may be due to the bronchial arterial communication with the fistula, disclosed by the operation. Either the systemic arterial connection may be sufficient to prevent unsaturation of blood or else the increased bronchial arterial pressure may alter and even reverse blood flow in an arteriovenous shunt. The absence of polycythemia in Case IX is explained by the chronic anemia.

Two patients (Cases I and VII) were admitted because of acute cerebral symptoms, one with a brain abscess and the other with acute meningoencephalitis. Neurologic disturbances are common in patients with pulmonary arteriovenous fistulas and have been usually attributed to cerebral anoxemia or to vascular thrombosis associated with the polycythemia.[1] However, as in Case I, brain abscesses are being found more frequently.[4,5,9,23,44]

Three patients (Cases IV, V and VIII) were asymptomatic. Two others (Cases II and VI, Table I) had diseases unrelated to the pulmonary arteriovenous fistulas which were incidental findings. Only the patient with dyspnea, cyanosis and clubbing of the digits and polycythemia (Case III) was poorly nourished. The heart and electrocardiogram were normal in all instances except Case II in which rheumatic heart disease was also present. The finding of a heart of normal size in patients with pulmonary arteriovenous fistulas is explained by the absence of increased pulmonary vascular resistance.[1,45,46]

Vascular bruits over the site of the pulmonary arteriovenous fistulas were heard in all but one patient (Case II). The murmurs varied from a faint systolic sound accentuated by deep inspiration to a loud harsh systolic blow; in one instance the bruit was present during diastole also. Accurate localization of the fistula by roentgenography in frontal and lateral views aided in eliciting the auscultatory signs.

Roentgen Features

The most constant finding in pulmonary arteriovenous fistulas is the presence of an abnormal shadow in the conventional chest roentgenogram.[24,34] The fistulas may vary in size and shape from minute circular densities (Figs. 2A and 5A) to large sharp oval lesions. (Figs. 1A, 6A and 9A.) Vague and ill defined edges may simulate pulmonary infiltrates. (Figs. 3A and 4A.) At times, localized increase of the hilar pulmonary vasculature may suggest an arteriovenous fistula (Figs. 7A and 8A), especially when lateral or oblique views indicate that the increased vasculature is related to the segmental or lobar pulmonary blood supplies. Another feature, the afferent pulmonary arterial and efferent pulmonary venous channels connecting with a pulmonary lesion, may be evident. (Figs. 1A and B, 2A, 6A and 9A.) Rarely, anomalous pulmonary venous drainage from the right lung into the inferior vena cava may simulate a pulmonary arteriovenous fistula.[47,48] Calcifications in pulmonary arteriovenous fistula are uncommon and have been reported in only three instances.[1]

Pulmonary arteriovenous fistulas may occur in any segment, subsegment or lobe. In our series the left lower and right middle lobes were involved respectively in two instances, while in the seven other cases the lesions were segmental. (Table I.)

Fluoroscopy permits recognition of vascular pulsation of pulmonary arteriovenous fistulas and their vascular connections, but in none of our cases was this phenomenon observed. More important are the changes in size of the lesions during respiratory maneuvers.[34] With the

Valsalva procedure (expiration against the closed glottis) the intrathoracic pressure is raised, blood flow diminishes in the thorax and the fistula becomes smaller. The Müller procedure (deep inspiration against the closed glottis) decreases the intrathoracic pressure and more blood fills the fistula and makes it larger.

Body section roentgenography has been highly recommended for the diagnosis of pulmonary arteriovenous fistulas.[1,24,34,44] In some instances it may be expected to supplement conventional roentgenography and disclose vessels connecting with the fistula. However, disease processes like bronchiectasis and chronic pneumonia may be exaggerated and reveal patterns that simulate pulmonary arteriovenous fistulas.[49]

In the roentgenographic differential diagnosis, primary or secondary lung tumors, bronchiectasis and tuberculosis are some of the conditions to be considered. One patient (Case II) was suspected of having a metastatic lung lesion because of the presence of a brain tumor. Bronchiectasis was diagnosed in Case III because of clubbing of the digits and haziness of the left lower lobe. Another patient (Case IV) was thought to have a left infraclavicular tuberculous infiltrate, while in Case VI a primary lung neoplasm or hamartoma was suspected.

Angiocardiography. There is general agreement that angiocardiography provides the definitive diagnosis of pulmonary arteriovenous fistulas.[1,2,24] Robb[50,51] first and Linskog and co-workers[36] later called attention to the importance of making large (14 by 17 inch) roentgenograms in order to prevent overlooking multiple and bilateral pulmonary arteriovenous lesions. Apparently, minute pulmonary telangiectasis may not be readily discernible by angiocardiography.[52] However, small arteriovenous fistulas in pulmonary segments are easily recognized. (Figs. 4, 5, 7 and 8.) The afferent and efferent vascular connections of pulmonary arteriovenous fistulas may be difficult to visualize with conventional roentgenography but are readily seen with angiocardiography. Multiple serial films are sometimes desirable for complete study of the lesion during the arterial and venous filling stages but usually two large films taken with a standard stereo-cassette changer[53,54] at 2½ and 6 seconds after the beginning of the injection will show the pulmonary arterial and venous components of the fistula. Involvement of the chest wall by pulmonary arteriovenous fistulas has been reported.[6] With angiocardiography this complication might have been recognized.

In the literature there are two reports of untoward reactions following angiography in patients with pulmonary arteriovenous fistulas. A fatality[55] occurred after the injection of 35 cc. of the contrast agent through a cardiac catheter with tip in the right atrium. Another patient[56] recovered after severe hemoptysis which followed injection of contrast material through a cardiac catheter placed in the main pulmonary artery. The recent report of rupture of the heart by injection of the contrast substance through a cardiac catheter during selective angiography[57] emphasizes the danger of injecting contrast substances directly into the cardiovascular system via catheters.

In marked contrast is our experience with the intravenous method of angiocardiography. In all, 2,573 injections of contrast material have been made in 1,939 patients during the period from October, 1946 to 1954. Only one death occurred, this in a fifty-six year old woman who had a pericardial effusion probably secondary to irradiation fibrosis. This record, in a series containing many patients seriously ill with heart and lung disease, fully justifies the use of angiocardiography, especially in pulmonary arteriovenous fistulas, for in this disease preoperative information in regard to bilateral or multiple involvement of the lungs is essential for the planning of the operation and conservation of lung tissue. In spite of recent warnings,[24] cardiac failure and/or hypertension are not contraindications to angiocardiography.

Treatment

There is general agreement that the best treatment for pulmonary arteriovenous fistulas is surgical excision of the lesions, with removal of as little lung tissue as possible in order to preserve pulmonary function, especially if multiple lesions are present. There are many reports in the literature of the disappearance of dyspnea, cyanosis and polycythemia following surgery.[1,12,15,16] Surgery is even advocated as a prophylactic measure in asymptomatic patients.[25] The risk of lobectomy or segmental resection is far less than the morbidity and mortality of complications like brain abscess,[4,5,9,23,44] hemoptysis[1,2,58] and cerebral thrombosis due to polycythemia.[1]

Too little time has elapsed to know if there will be recurrence of pulmonary arteriovenous

fistulas in other portions of the lung after surgery. Two cases are on record[1] in which pre-existing pulmonary arteriovenous fistulas enlarged after surgical excision of associated pulmonary fistulas. The recent finding of multiple minute pulmonary telangiectasis on lung biopsy[52] indicates the futility of lung surgery in such a condition.

SUMMARY

Pulmonary arteriovenous fistulas are hereditary hemangiomatous malformations of the pulmonary vascular bed. Almost 40 per cent of the reported cases also have hemangiomas elsewhere in the body, indicating that a close relationship to familial hemorrhagic telangiectasis (Rendu-Osler-Weber's disease) exists.

When pulmonary arteriovenous fistulas are large and do not have systemic arterial connections, dyspnea, cyanosis, clubbing of the digits and polycythemia result from unsaturation of the blood. Hemoptysis may occur when there is rupture of the paper-thin pulmonary vascular anomaly. There is also a high incidence of cerebral symptoms due either to cerebral thrombosis, secondary to the polycythemia, or to infection, especially brain abscess. The heart remains normal in size because pulmonary arteriovenous fistulas do not cause increased pulmonary vascular resistance.

In our series of nine cases the classical syndrome of cyanosis, clubbing of digits, polycythemia and a vascular murmur heard over the pulmonary fistula was present in one case only. One patient with dyspnea, fatigue and familial telangiectasis had bilateral pulmonary arteriovenous fistulas; chronic anemia prevented intense cyanosis and polycythemia. In three instances the patients were asymptomatic; in two the pulmonary arteriovenous fistula was an incidental finding; in the remaining two, acute cerebral conditions (brain abscess and meningoencephalitis) were the presenting symptoms. Vascular bruits were heard in eight patients. All patients had abnormal chest roentgenograms.

The diagnosis of pulmonary arteriovenous fistula can often be made by conventional roentgenography, particularly if the index of suspicion is high. Pulmonary densities with hilar vascular connections localized in lobes or segments of the lung, or increased hilar vascularities, should arouse suspicion of an arteriovenous fistula. Change in size of the lesions after respiratory maneuvers (Valsalva, Müller) and delineation of the afferent arterial and efferent venous connections by body section radiography may be confirmatory. Angiocardiography, however, establishes the diagnosis and is recommended for preoperative evaluation.

The treatment of pulmonary arteriovenous fistulas is surgical excision, with preservation of as much lung tissue as possible in order to preserve pulmonary function, especially if multiple lesions are present. Surgery is usually curative. It is recommended by some even in the asymptomatic case since the risk of brain abscess, fatal hemoptysis or development of cerebral thrombosis when polycythemia occurs is far greater than the morbidity and mortality of lobectomy or segmental resection.

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Pulmonary Lesions in "Rheumatoid Disease" with Remarks on Diffuse Interstitial Pulmonary Fibrosis*

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"RHEUMATOID disease" is a more descriptive term than rheumatoid arthritis since it expresses a widespread affliction involving not only the locomotor system but also other parts of the body.[1] For reasons to be given later, there is much to recommend this all-inclusive designation and it will be used in this sense in the following pages.

In 1948 Gruenwald[2] described a case of "rheumatoid disease" with visceral lesions and commented that this combination had not been reported previously except for passing mention of nodules in subcutaneous tissues, skeletal muscles and nerve trunks, also scars of rheumatic heart disease. The case cited was found to have granulomatous lesions in the heart, pleura and capsule of the spleen, indicating that all serous membranes may be involved. The Ninth Rheumatism Review,[3] published in 1948 and containing a comprehensive summary of the English and American literature on the subject, refers to studies by Baggenstoss, Rosenberg and Hench[4,5] in which are described thirty cases of "rheumatoid disease" examined at autopsy. A high incidence of cardiac lesions, indistinguishable from those of rheumatic fever was found, also a relative frequency of microscopic renal lesions. Although pneumonia, chronic suppuration, embolism and massive collapse of the lung were the most common causes of death, the authors could find no distinguishing pulmonary lesions which could be correlated with the "rheumatoid disease." Nor could they find any relationship with the frequent finding of fibrous pleural adhesions which were present in twenty-two of the thirty cases. The Tenth Rheumatism Review, published in 1953,[6] contains three references[7–9] in which are described five cases of "rheumatoid disease" with pulmonary findings. In 1954 Harris[10] was able to collect references to a total of twenty cases of pulmonary lesions associated with "rheumatoid disease" and cited a case of his own. Five of these cases were studied at autopsy, two by Ellman and Ball and three by Christie.[11] Two additional cases, with autopsy examinations showing pulmonary lesions, have been reported, one by Bevans and co-workers[12] and the other by Katz and Auerbach.[13] The literature on the subject appears to be growing rapidly.

With increasing use of routine chest roentgenography, changes are being discovered in the lungs of patients with "rheumatoid disease" indicating that these organs are involved quite frequently and early in the course of the disease. Inasmuch as the lungs, as visualized in chest x-rays, often serve as mirrors of what is going on in other parts of the body,[14] roentgenography offers a useful means of investigation of obscure systemic diseases associated with pulmonary manifestations. Points of similarity or dissimilarity between diseases, featured by lung changes which are demonstrable roentgenologically, are often easily recognized and the significance of such changes, at times, better appreciated in serial chest x-rays in the light of the clinical findings than at autopsy. As to the applicability of chest roentgenography to the study of pulmonary manifestations of "rheumatoid disease" and to related collagen diseases, it may be pointed out that the lungs possess a dual blood supply, an immense interstitial stroma and a broad pleural serosa, tissues which are most expressive of mesenchymal disorders.

Within a space of two months the writer had occasion to observe three patients with acute

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"rheumatoid disease" with characteristic articular manifestations in whom the chest x-ray findings were in keeping with a systemic disturbance. In two cases it was possible to obtain lung biopsies for histologic study. Since the roentgenologic and pathologic findings in the cases studied resembled in some respects those seen in several other members of the collagen group of diseases, also in occasional instances of diffuse interstitial fibrosis of unknown etiology, reference will be made to pertinent findings in these groups of cases. The last mentioned is currently being studied by Lubliner and the writer.[15]

CASE REPORTS

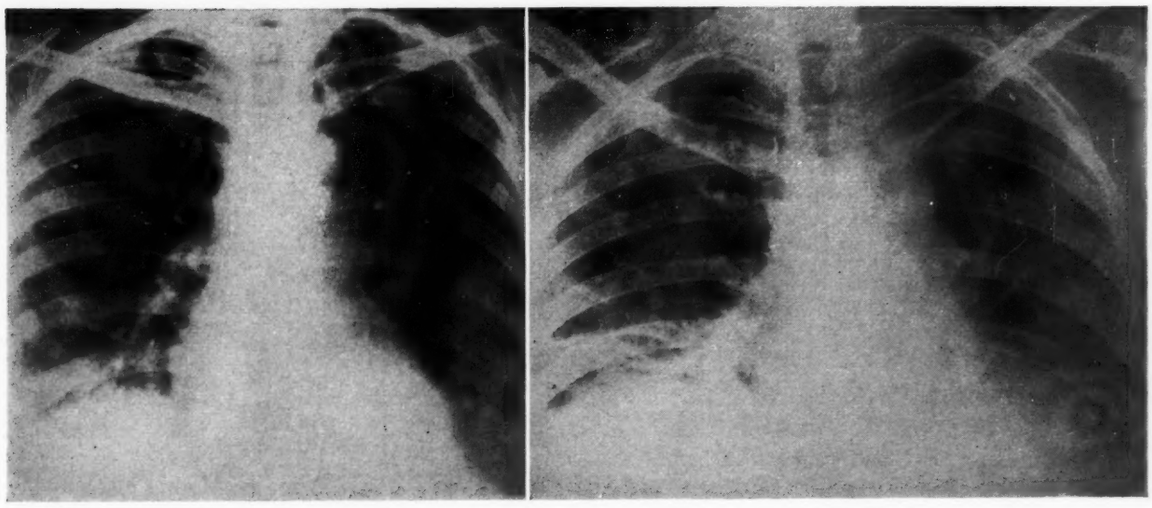
CASE 1. A. R., a forty-nine year old white female, was subject to frequent upper respiratory infections as a child. Repeated chest x-rays failed to reveal any abnormalities. At the age of twenty-eight the patient had an ovary, fallopian tube and appendix removed. She continued to have her menses regularly. In July, 1949, the patient developed symptoms which were ascribed to pneumonia. A chest x-ray revealed faint haziness in both lower lobes but no distinct parenchymal involvement. The condition cleared with penicillin treatment. During the following two years the patient experienced menopausal symptoms for which she received hormonal treatment.

In June, 1952, after an emotional disturbance, the patient developed generalized urticaria of the hands and face, with swelling and pruritus, also pain, redness and swelling of the joints beginning in the toes and spreading to the ankles, upper extremities and other joints. The patient also experienced deep muscle pain. The menses ceased abruptly. On August 23, 1952, the patient was hospitalized for treatment of her "rheumatoid disease." Chest x-rays showed no significant changes from those noted three years previously. (Fig. 1A.) The patient was treated with salicylates and discharged after a week, somewhat improved.

Two months later there was recurrence of rheumatoid symptoms and at this time the patient complained of shortness of breath which seemed worse during the periods of aggravation of the joint pains. In January, 1953, because of increasing severity of the arthritic symptoms, the patient was again hospitalized. In addition to the dyspnea and joint pains, there were now present anemia, four-pillow orthopnea, an enlarged liver and ankle edema. A chest x-ray disclosed, for the first time, soft irregular mottlings in both lungs; also diffuse, interstitial striations, especially in the lower lobes, possibly a small amount of fluid at both bases and prominence of the horizontal fissure on the right. The right leaf of the diaphragm was displaced upward. (Fig. 1B.) Repeated chest x-rays taken during the following months showed no significant changes except for greater accentuation of the interstitial striations and less soft mottling. The patient was treated with digitoxin, iron and cortisone. The swelling, redness and pain disappeared from the hands. For about nine months the patient continued to take cortisone periodically, also mercurials and salicylates to relieve the joint pains.

In December, 1953, the joint symptoms recurred and the patient was rehospitalized. On this occasion she was given penicillin but developed a generalized urticaria and was given cortisone for relief. A chest x-ray showed accentuation of the diffuse pulmonary infiltrations. Several weeks later the patient was admitted to the New York Hospital. Cardiopulmonary functional tests were performed in this institution and the results, furnished through the courtesy of Dr. I. Steinberg, revealed the following: Cardiac catheterization showed moderate pulmonary arterial hypertension compatible with diffuse pulmonary fibrosis. An angiocardiogram revealed compression of the pulmonary vessels and slight enlargement of the pulmonary artery suggestive of elevated pulmonary artery pressure. The left ventricle was slightly enlarged. Pulmonary function tests revealed impairment of ventilatory capacity indicative of pulmonary fibrosis of a diffuse variety. Other laboratory findings were similar to those obtained several months later at the Montefiore Hospital where the patient was admitted on February 27, 1954, and remained until discharge March 20, 1954.

The patient appeared chronically ill, dyspneic even at rest, and complained of generalized joint pains requiring salicylates and sedation. The temperature was 99.6°F., pulse 120 and regular, respiratory rate 20 and blood pressure 130/90. The skin of the face revealed a macular erythema more marked over both cheeks. The thyroid was not enlarged; there was no venous distention. The extremities showed moderate fusiform enlargement of the interphalangeal joints of the hands and wrists which were puffed and painful on motion. A slight deformity of the right hand was ascribed by the patient to long-



1A 1B

FIG. 1. (Case 1.) A, August 25, 1952; faint haziness over both lower lung fields; possibly pleural reaction at bases. B, chest x-ray, February 16, 1953; soft irregular mottlings throughout both lung fields and faint reticular infiltrations; prominent horizontal fissure on right; possibly small collections of fluid at bases; right leaf of diaphragm displaced upward.

standing ulnar nerve injury. The knees and ankles were also swollen and painful. There was impaired percussion over both lower lobes, especially over the right base. Auscultation revealed rales over the entire chest, chiefly posteriorly, and at the bases where a coarse friction rub could be heard. The friction rub was present throughout the patient's stay at the hospital and in follow-up examinations. The heart rate was regular with a soft systolic murmur at the left border. P_2 was accentuated. The liver was palpable three finger breadths below the right costal margin and was not tender. The spleen was not felt.

Chest x-rays showed accentuation of diffuse interstitial striations throughout both lung fields but, on the whole, the changes were similar to those seen in previous films. (Fig. 1C.) X-rays of the hands, shoulders, feet and other joints revealed moderate osteoporosis, especially of the hands, narrowing of joint spaces but no erosion. Laboratory data included: urine negative; hemoglobin 11 gm. per cent; red blood cells 4,500,000 per cu. mm.; white blood cells 8,050 per cu. mm. with a normal differential. Erythrocyte sedimentation rate was elevated; no lupus erythematosus cells in the peripheral blood. Serum albumin 3.6 gm. per cent, serum globulin 4.2 gm. per cent. An electrocardiogram showed old posterior wall infarction with right bundle branch block. Basal metabolism +47 per cent; repeated +34 per cent; cephalin flocculation

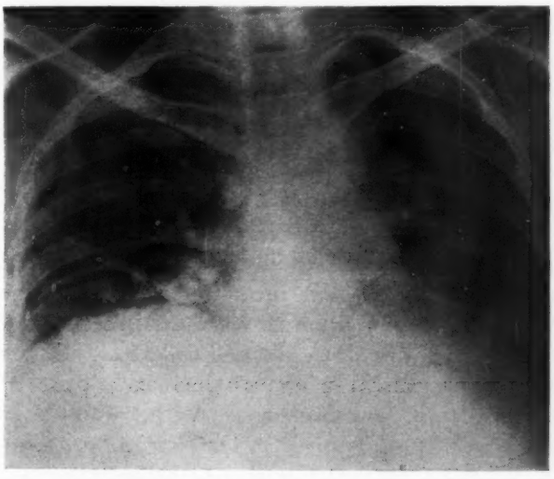
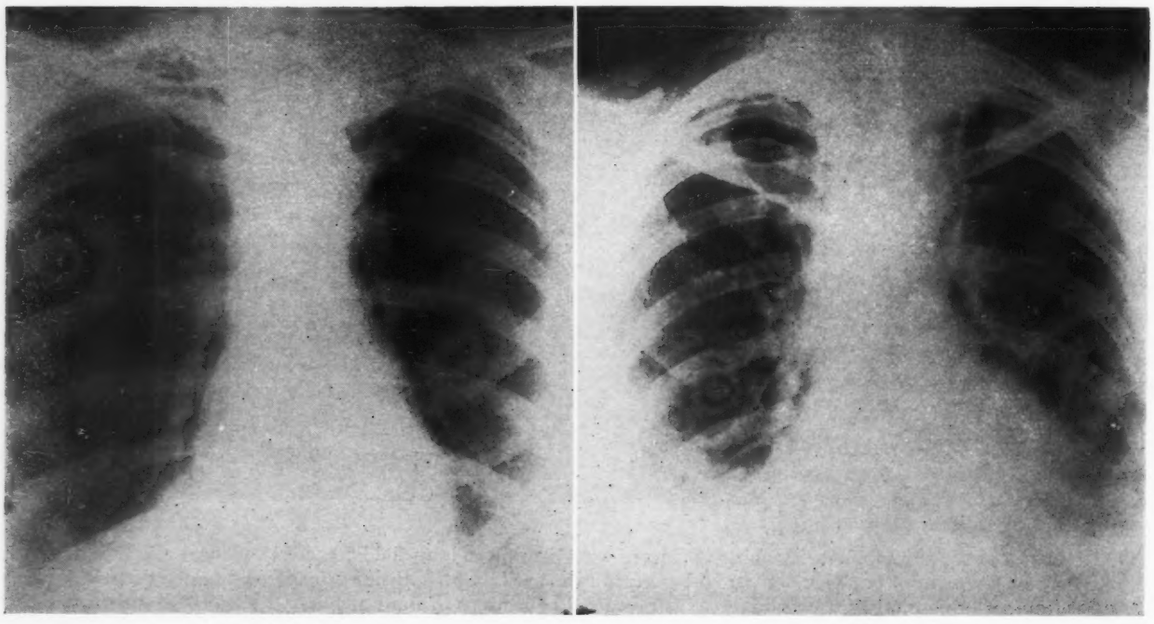


FIG. 1C. Chest x-ray (Case 1), February 23, 1954; diffuse interstitial striations throughout both lung fields; irregular density, left lower chest.

1+, thymol turbidity 18. Other blood examinations showed no significant findings. Repeated examination of the sputum failed to reveal acid-fast organisms. Skin and muscle biopsies which had been obtained previously at the New York Hospital had shown no abnormalities.

The patient continued to have dyspnea, worse when the joint pains were more severe. Salicylates and sedatives gave partial relief. Prior to the institution of hormonal treatment spirometry was done. The vital capacity was 1,000 cc. with a maximum breathing capacity of 43 L. per minute. After ten days' treatment with corti-



2A 2B

FIG. 2. (Case II) A, chest x-ray, October 18, 1949; scattered calcific foci in left lung and thickened pleura on that side; the right lung field is clear. B, chest x-ray, May 21, 1954. In addition to calcified foci in left lung seen in previous chest x-rays, there are now diffuse interstitial striations in both lungs, especially the right lung; there was pleural reaction at both bases.

cotropin the vital capacity rose to 1,800 cc. and the maximum breathing capacity to 73 L. per minute. The patient improved symptomatically and was able to knit which she could not do previously. The linear infiltrations in the lungs appeared slightly less pronounced but, on the whole, the x-ray findings were unaltered. After discharge from the Montefiore Hospital the patient continued to receive decreasing doses of corticotropin supplemented with, and later replaced by, cortisone. After four months the hormonal treatment seemed to be decreasingly effective and the patient required salicylates to relieve the joint pains, also inhalations of vaponefrin to relieve the paroxysms of dyspnea. At the time of this writing (August, 1954) the disease appears to be slowly progressive. The patient has lately noted a rash over the upper chest and arms associated with itch at the time of recurrence of joint pains and dyspnea.

CASE II. H. D., a fifty-eight year old white female, was found to have pulmonary tuberculosis of the left upper lobe at the age of thirty-two. The disease underwent spontaneous arrest. Thirteen years later the disease relapsed and the sputum contained acid-fast bacilli. A pneumothorax was induced on the left side and after one year of collapse therapy the lung was released. Following this the patient felt well and attended to her household duties. Repeated chest x-rays showed a calcified scar in the left apex, scattered calcific foci in the left upper lobe and a thickened pleura on that side. (Fig. 2A.) The sputum was repeatedly negative for acid-fast bacilli.

In November, 1952, the patient developed pain in the right lower chest associated with slight cough but no fever. A chest x-ray disclosed soft irregular infiltrations at the right base suggestive of pleurisy or atypical pneumonia rather than reactivation of tuberculosis. The remainder of both lung fields was unchanged. Sputum examinations continued to be negative for acid-fast bacilli. The patient was treated with aureomycin and penicillin. On one occasion she received sulfonamide but developed a skin rash and itch on the tenth day and the medication was discontinued. The rash cleared spontaneously in about two months but recurred in mild form on later occasions. In December, 1952, the patient had a recurrence of right-sided chest pain, less severe than the first episode, and she was treated with bed rest alone.

In April, 1953, as the chest pain was receding, the patient developed painful swellings of joints, beginning at the wrists and spreading to the

elbows, shoulders and spine. The skin felt hot and there was pain on motion. The patient was treated with salicylates during the following year. On April 26, 1954, the patient consulted the writer because of recurrence of chest pain and rheumatoid symptoms. At this time she also had cough, night sweats, fever and general malaise. She had noticed dyspnea shortly after the onset of the original pleurisy which had become progressively worse. The patient stated that she had always been in good health except for a transient period of hypertension during her menopause. Except for the urticarial reaction after the administration of sulfonamide, the patient had had no other stigmata of hypersensitivity. A chest x-ray now revealed diffuse reticulations throughout both lung fields with evidence of a pleural reaction at both bases, in addition to the evidence of inactive tuberculosis noted previously. (Figs. 2B and 2C.) In view of the past history of tuberculosis, the patient was given 300 mg. isoniazid daily to note whether the drug would have any effect on the joint symptoms. At the end of two weeks the patient complained that the rheumatic pains had become worse and the medication was discontinued.

The patient was admitted to the Montefiore Hospital on May 27, 1954. Physical examination revealed a sallow, chronically ill woman somewhat dyspneic even at rest. The temperature was 100°F., pulse 100, respiration rate 20 and blood pressure 140/80. The interphalangeal joints of the fingers, also the wrists, elbows and shoulders, were swollen and painful on motion. The joints of the lower extremities were not affected. Examination of the chest disclosed the heart to be slightly enlarged, rhythm irregular with no murmurs. Auscultation of the lungs revealed many rales at both bases. A pleural friction rub was heard posteriorly, chiefly over the right lower chest.

Chest x-rays revealed the findings noted previously. X-rays of the hands and elbows revealed moderate osteoporosis of the bones of the carpus and swelling of the surrounding soft tissues. There were no productive arthritic changes. An electrocardiogram showed right axis deviation and multiple premature beats of the ventricle. Other laboratory findings were Mantoux 2+in 1:100 O. T. dilution, hemoglobin was 10 gm. per cent, red blood cells 3,710,000 per cu. mm., white blood cells 7,750 per cu. mm. with a normal differential The erythrocyte sedimentation rate was accelerated. Serum albumin was

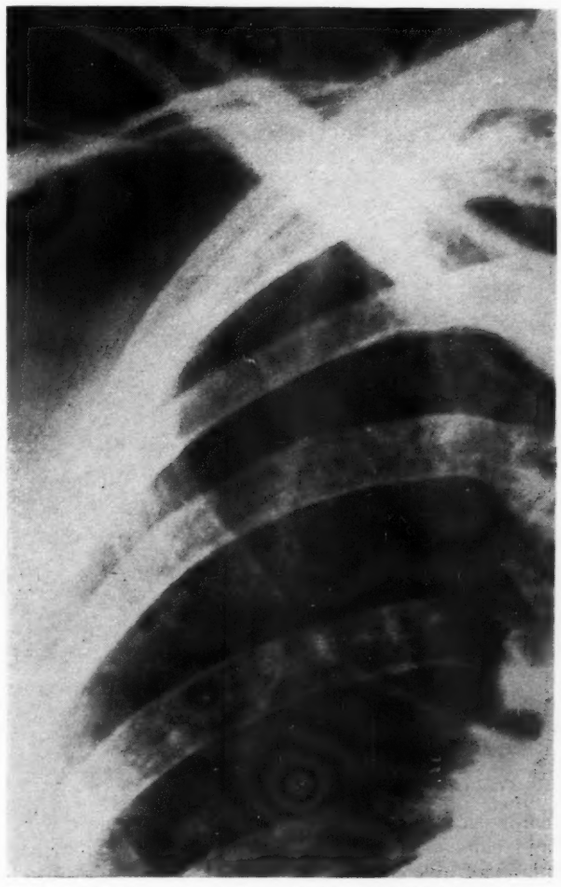


FIG. 2C. Chest x-ray (Case II), May 28, 1954; enlargement showing detail of right upper lobe.

4.2 gm. per cent, serum globulin 3.3 gm. per cent, fasting blood sugar 90 mg. per cent, blood urea nitrogen 11.2 mg. per cent, uric acid 4.6 mg. per cent, serum calcium 10 mg. per cent, serum phosphorus 3.4 mg. per cent, serum cholesterol 232 mg. per cent, L.E. preparations of the blood were negative, liver function tests, cold agglutinins and routine serologic tests were also negative. Repeated examinations of the sputum failed to reveal the presence of acid-fast bacilli.

Because of the persistence of joint pains and low-grade fever which did not respond to salicylates, it was decided to give the patient a trial of cortisone. Prior to the administration of the latter, a biopsy of the right lower lobe was done by Dr. Morris Rubin on June 10, 1954. The specimen was examined by Dr. J. Hasson. The findings were as follows: the pleural surface of the specimen was focally covered with fine adhesions. The pleura was noted to move freely on the underlying lung parenchyma suggesting

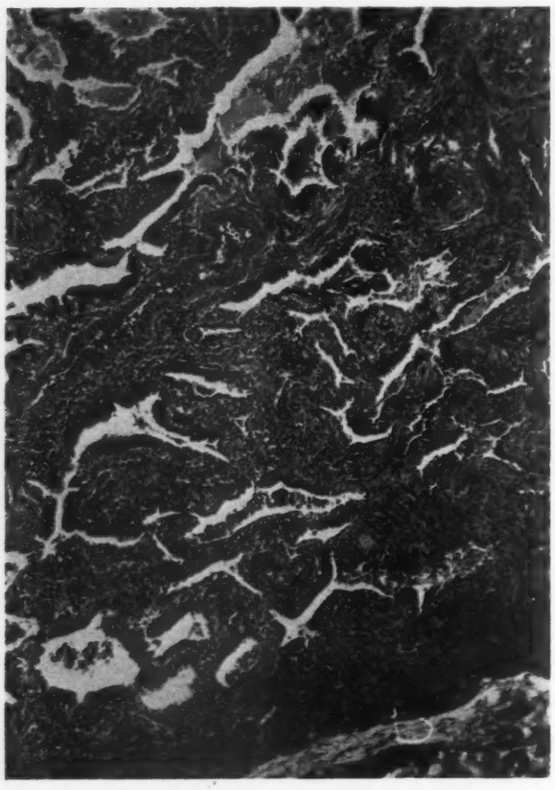


FIG. 2D. Lung biopsy (Case II) showing marked thickening of interalveolar septa; distortion, narrowing and elongation of remaining alveolar spaces; hyperplasia of alveolar lining cells; thickened wall of blood vessel seen in upper right field.

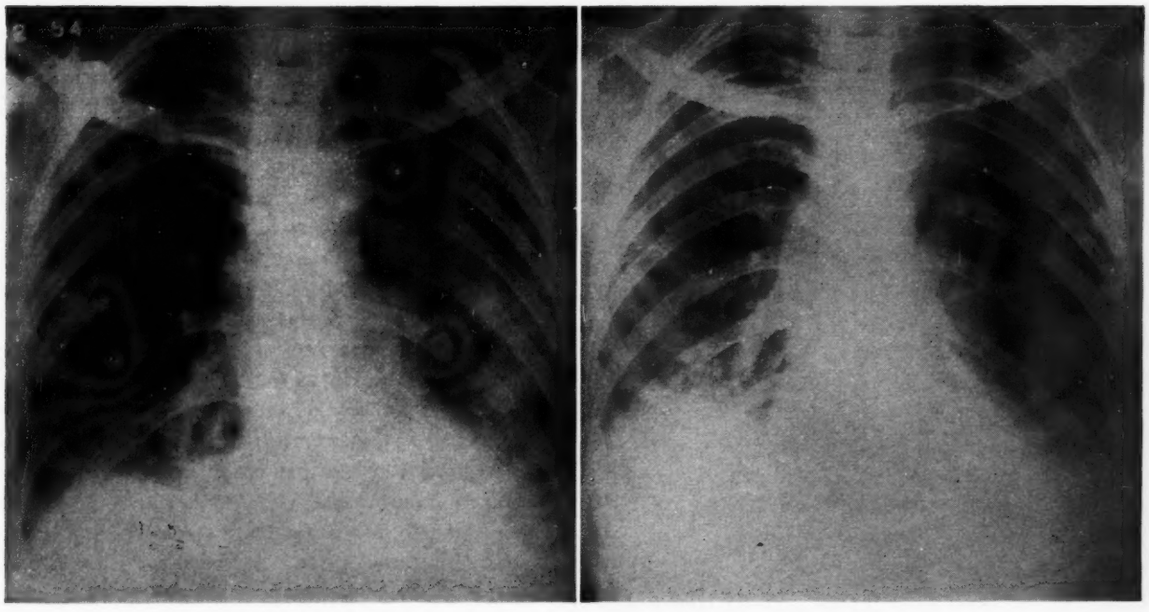
edema of the subpleural connective tissue. On section the parenchyma appeared collapsed and gray-pink with focal specks of anthracotic pigment. One area of hemorrhage was encountered which was fairly discrete and round and measured 0.6 cm. in diameter. Another focal area appeared as solidified parenchyma suggestive of consolidation. This area appeared gray-white and poorly defined.

Microscopic examination disclosed a markedly altered pulmonary parenchyma with marked fibrosis of the alveolar septa and distortion of the alveolar spaces. (Fig. 2D.) These spaces were focally lined by a cuboidal epithelium and filled with a mucinous exudate containing mononuclear cells. The interstices were thickened by an increased amount of fibrous tissue and a scattered exudate of mononuclear cells consisting mainly of lymphocytes and scattered plasma cells and histiocytes. The density of this exudate varied from zone to zone. In some areas small dense aggregates of lymphocytes were seen in the interstices. Occasional bronchioles were seen which contained plugs of mucinous material containing mononuclear cells including exfoliated epithelial cells. No intact lung parenchyma was seen in any of the sections. There was no evidence of tuberculosis. The blood vessels showed a patchy, hyperplastic sclerosis of the small arteries and special stains disclosed that this was due mainly to subintimal fibrosis with a lesser element of hyperplasia of the media. Thin, vascular, fibrous adhesions were seen attached to the pleura which was somewhat thickened. The diagnosis was diffuse interstitial fibrosis of the lung with hyperplastic sclerosis of small arteries.

The patient was discharged from Montefiore Hospital on June 16, 1954, slightly improved. Late in June, 1954, the right knee and both ankles became swollen and painful. The patient was given cortisone 100 mg. daily and after one month there was considerable symptomatic improvement. Auscultation still revealed a pleural friction rub, less marked than on previous examinations; other physical findings were unchanged. Chest x-rays in August, 1954, have shown slight regression in the diffuse interstitial markings.

CASE III. E. T., a forty-six year old Negro female, became ill on December 20, 1953, with fever, cough and dyspnea, also painful, swollen joints. The patient was bedridden at home for two weeks and was treated with penicillin. Although not fully recovered, she returned to work as a domestic. On February 20, 1954, there was a return of fever, cough and painful joints; at this time, the patient also had chest pain and, on one occasion, spat up a small amount of blood. The patient was hospitalized on March 11, 1954. Examination revealed an acutely ill, dyspneic woman; temperature 103°F., pulse 110, respiration rate 24 and blood pressure 100/80. Both hands, especially the left, showed fusiform, tender swellings of the interphalangeal joints. The right knee was also swollen and tender. Examination of the chest revealed dullness over both sides and rales at the bases. The heart revealed no abnormal findings. The diagnosis was bilateral bronchopneumonia and rheumatoid arthritis; or, possibly, acute rheumatic fever and rheumatic pneumonia.

Chest x-rays revealed irregular, patchy infiltrations throughout both lungs, chiefly the left, in keeping with acute bronchopneumonia; there was a pleural reaction at the bases. The heart was not enlarged. (Fig. 3A.) X-rays of the hands showed fusiform swelling of the interphalangeal



3A 3B

FIG. 3. (Case III) A, chest x-ray, March 12, 1954; irregular, patchy infiltrations in both lower lobes, more numerous on the left where there is confluence of densities in the mid-lung field; there is pleural reaction at bases. B, chest x-ray, May 13, 1954; fine, diffuse reticulations permeating both lungs, chiefly the right; pleural reaction at bases more evident.

joints. The joints themselves were not involved. Laboratory tests revealed an accelerated erythrocyte sedimentation rate, hemoglobin 79 per cent, red blood cells 4,220,000 per cu. mm., white blood cells 8,700 per cu. mm. with a normal differential; urine was negative; the Mazzini test was negative; serum albumin was 3.2 gm. per cent and serum globulin 3.2 gm. per cent; an electrocardiogram showed no abnormalities. The patient was treated with combined antibiotics, later with penicillin alone, also salicylates and sedatives. After one month of penicillin treatment the patient developed a generalized rash which gradually subsided. It was ascribed to penicillin sensitivity. Although the chest x-rays after three weeks showed considerable clearing of the lung fields, the rales persisted. The joint pains slowly abated, the fever declined and the patient was discharged on April 24, 1954.

Six days later the patient was admitted to the Morrisania City Hospital because of recurrence of fever, cough, chest and joint pains. The patient was acutely ill and dyspneic. The rash was still present over the chest and upper arms. The fingers, toes and knees were swollen and painful on motion. No abnormalities were found in the heart. On auscultation numerous rales were heard in both lungs, with pleural friction rub at the right base. The hemoglobin ranged between 8 and 11.4 gm. per cent, red blood cells 2,500,000 per cu. mm., white blood cells ranged between 5,800 and 10,000 per cu. mm. with a normal differential. The erythrocyte sedimentation rate was accelerated. The sputum was negative for acid fast bacilli. Mazzini test ±, Wassermann test 4+, urine was negative, serum albumin 2.6 gm. per cent, globulin 3.5 gm. per cent, cholesterol 97 mg. per cent, blood urea nitrogen 8.0 mg. per cent, fasting blood sugar 78 gm. per cent, cholesterol esters 165 gm. per cent, uric acid 1.5 mg. per cent, bilirubin 0.14 mg. per cent, thymol turbidity 15 units, cephalin flocculation 1+. Blood cultures were repeatedly negative for growth. Agglutination of the typhoid, paratyphoid group was negative. Chest x-rays now revealed fine diffuse interstitial striations throughout both lungs, especially the right, and less of the pneumonic exudate seen in previous films; a pleural reaction was present at the bases. (Fig. 3B.) The patient continued to have low-grade fever. On salicylate therapy the joint pains gradually subsided and the patient was discharged on May 26, 1954.

The patient was readmitted to the Morrisania City Hospital on July 1, 1954, because of recurrence of pain in the hands, wrists, shoulders and ankles, with swelling of the affected parts. The

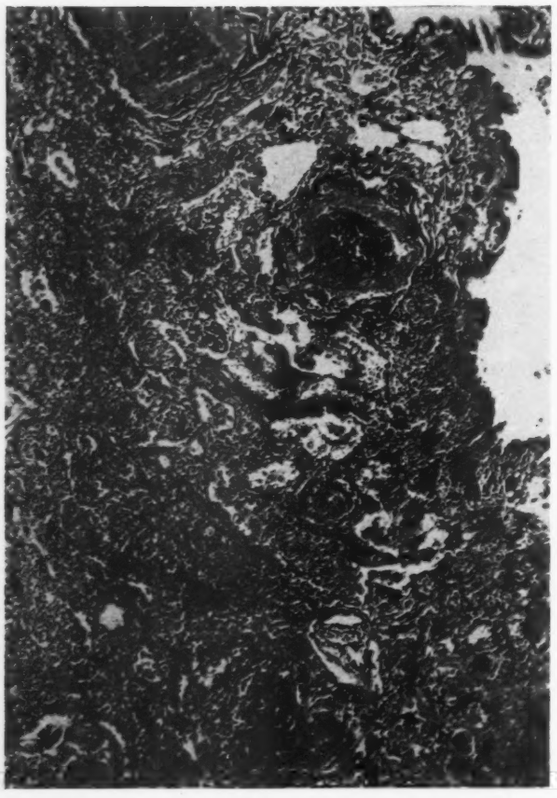


FIG. 3C. Lung biopsy (Case III) showing organizing and interstitial pneumonitis with patchy areas of fibrosis; several prominent blood vessels are seen.

patient was dyspneic and complained of a feeling of chest oppression. Physical and x-ray examinations revealed few changes from those noted previously. The laboratory findings were little changed. On July 2, 1954, a biopsy of the right lower lobe was done by Dr. M. Rubin. The excised specimen was examined by Dr. R. Lubliner. The findings were as follows: The lung was somewhat firmer than normal but fairly well aerated, the pleura slightly thickened. Cut section revealed pinkish-red parenchyma through which were scattered small strands of depressed, grayish tissue.

Microscopic examination showed marked alteration of normal architecture, foci of well aerated parenchyma alternating with foci of atelectasis. (Fig. 3C.) There was thickening of interalveolar septa due to increased vascularity, cellular infiltration and patchy fibrosis. In many instances there was hyaline thickening of the walls of the small vessels within the septa. The cellular infiltration was monocytic with a large number of plasma cells. There was marked hyperplasia of the alveolar lining cells. In other parts the alveolar spaces were not only distorted but elongated and narrowed due to the septal thickening and also to an organizing pneumonia. The alveolar spaces were filled with an admixture of fibrin, monocytes, alveolar macrophages and, in many instances, completely obliterated by the organized exudate. Both processes together caused scattered patches of pulmonary fibrosis; however, this in itself was not yet a prominent feature. There was slight fibrous thickening of the pleura and of the interlobular septa. There was moderate thickening of the interalveolar septa, also in well aerated areas. The diagnosis was interstitial and organizing pneumonitis with patchy pulmonary fibrosis.

The patient was treated with salicylates and sedation. The joint pains gradually subsided although the patient still had a low-grade fever at the time of her discharge to the Chest Clinic on July 23, 1954. A chest x-ray taken a week later showed slight decrease in the pulmonary markings. The pleural reaction was still present at both costophrenic sinuses. The patient still had painful and swollen knees and ankles and the fingers "felt tight" especially on arising.

PREVIOUSLY REPORTED CASES WITH AUTOPSIES

Ellman and Ball (1948)[7]: A forty-seven year old male had pleurisy progressing to empyema at eleven years of age. "Rheumatoid disease" appeared two and one-half years prior to present illness. Chest x-ray revealed fine reticulations throughout both lung fields with a chronic bronchopneumonia process. After admission to the hospital the patient developed cough, expectoration and, soon, thereafter, generalized purpura, pyrexia, dyspnea and cyanosis. The patient died three months after onset of the respiratory symptoms. Autopsy revealed dense pleural adhesions, interstitial fibrosis and pneumonitis with terminal bronchopneumonia, also some small abscesses; the blood vessels were largely normal.

Ellman and Ball (1948)[7]: A forty-eight year old female had recurring bronchitis. History revealed acute polyarthritis eight months prior to acute respiratory symptoms. Examination showed a rash over the arms and trunk. Chest x-ray showed bilateral basal opacities indicative of consolidation and marked reticular shadows extending into the mid-zones. The patient was treated with penicillin for suspected pneumonia without effect. She died one year after the onset of the "rheumatoid disease." Autopsy revealed

interstitial fibrosis and pneumonitis with terminal bronchopneumonia, also minute abscesses containing pus. The blood vessels showed no changes.

Katz and Auerbach (1951)[13]: A fifty-year old male with a history of asthma in childhood had increasing dyspnea, intermittent fever and weakness for about two years when he developed migratory polyarthritis and two months later cough and expectoration. Examination revealed advanced "rheumatoid disease" with demineralization of osseous structures, flexion and contracture deformities of hands, as well as muscular and subcutaneous atrophy of the parts. A chest x-ray four months after the appearance of the "rheumatoid disease" revealed diffuse, finely mottled and patchy nodular infiltrations throughout both lung fields. Later chest x-rays showed clearer definition of interstitial infiltrations. The patient showed iodide sensitivity when this drug was administered. He died in congestive heart failure. Autopsy revealed diffuse interstitial fibrosis of lungs with emphysema giving the organs a spongy appearance.

Bevans, Nadell, Demartini and Ragan (1954)[12]: The authors report the case of two patients with "malignant rheumatoid arthritis" whose fulminating course was characterized by widespread granulomatous lesions in the pleura, pericardium, heart, diaphragm, synovia, kidneys and lungs. In one patient the lungs at autopsy revealed compression of alveolar spaces but otherwise the parenchyma appeared normal. The other case, a forty-six year old female with "rheumatoid disease" of fifteen years' duration, developed pericarditis, pleuritis and eventually generalized anasarca. At autopsy several small yellow nodules were found in the left upper lobe which were soft and necrotic, also a solitary subpleural tubercle. Microscopically, the yellow nodules did not resemble tuberculosis, rather granulomas with necrotic centers. Fibrinoid material filled the alveolar spaces. Acid-fast and bacterial stains of these lesions were negative for organisms.

Christie (1954)[11]: A forty-seven year old male had rheumatoid symptoms since the age of thirty-five. Six days before the patient's first admission to the hospital he developed dyspnea, anorexia and edema of the legs. A right pleural effusion was aspirated. The patient was readmitted thirteen months later with cough and progressive edema. He died two months later. Autopsy showed fluid in both pleural cavities. The pleura was covered by fibrin. Several subpleural nodules were present but the intervening lung tissue was normal. Microscopic examination showed nodular lesions with spreading foci of fibrinous pneumonia undergoing central necrosis. At the edge of the necrotic foci the alveoli were filled with fibrin and the adjacent lung showed thickening of septa.

Christie (1954)[11]: A sixty-seven year old male developed rheumatoid symptoms and chest pain six months before admission to the hospital. At this time the patient had dyspnea, ankle edema and swollen joints. A chest x-ray showed cardiac enlargement, pulmonary congestion and fluid at the lung bases. Pleural aspiration revealed sterile fluid. The patient died twenty days after admission. Autopsy showed fibrous pleural adhesions, also fine fibrosis in the lung substance. Microscopic examination revealed radiating loose connective tissue. The scars appeared to be growing actively. The inner part of each was less cellular, with coarser collagen, whereas peripherally the collagen was fine and small round cells and fibroblasts were numerous. At the spreading edge the septa became thickened and encroached on the alveolar spaces and were gradually taken up in the scar.

Christie (1954)[11]: A fifty-three year old female had recurring seizures of pain which had the characteristics of Raynaud's syndrome. The presenting complaints were shortness of breath, cough and expectoration which had been present for three months. The patient revealed advanced rheumatoid disease of the joints. On a subsequent admission a right pleural friction rub was heard. The chest x-ray showed a round dense shadow 6 cm. in diameter in the right upper lobe. There was increasing emaciation and death. Autopsy revealed extensive adhesions obliterating the left pleural sac and also adhesions over the lateral aspect of the right lung. There was a firm rounded mass 7 cm. in diameter occupying the lower half of the right upper lobe. It was composed of pale, dry, friable tissue in which remnants of bronchi were identifiable. The mass was encapsulated by a layer of dense fibrous tissue. The remainder of the lung was normal except for old apical pleural scars. Microscopic examination revealed the massive lesion in the right upper lobe to be indistinguishable in structure from that of a subcutaneous periarticular nodule of rheumatoid arthritis. At the border of the scar the alveolar septa of the pulmonary tissue were thickened.

For the sake of completeness, Christie's lucid description of the pathology of the pulmonary lesions in "rheumatoid disease" is worth citing. This investigator notes that the pulmonary lesions in rheumatoid disease are as varied and widespread as those in other organs. They range from acute exudative foci to scars of loose or dense texture. In the cases studied, the pleura was found to be a prominent site but lesions were demonstrable in all parts of the lungs including the parenchyma, bronchi and lymphoid tissue. Christie describes the histologic appearances of the pulmonary lesions in "rheumatoid disease" as follows:[11] (1) proliferation of mononuclear cells in the alveolar septa with occasional binuclear formation in the early stages; (2) sharply localized areas of fibrinous pneumonia constituting a more severe grade of parenchymatous lesion. This might proceed to necrosis and softening or to organization; (3) connective tissue "buds," resembling those described by Masson and by Neubuerger and co-workers in rheumatic pneumonia, are sometimes present. These consist of minute nodules of connective tissue lying in alveolar ducts, budding from the wall; (4) focal scars of variable density in the pleura, alveolar walls, bronchi, vessels and peribronchial and perivascular connective tissue. Much of the fibrosis is non-specific although such areas usually contain more advanced foci recognizable as "rheumatoid" nodules; (5) focal scarring or diffuse fibrosis in the walls of the smaller pulmonary vessels and of the bronchial arteries; (6) acute fibrinous pleurisy and chronic pleural scarring independently of or in association with other pulmonary changes.

The autopsy findings in the cases of Ellman and Ball[7] showed evidence of advanced bronchopneumonic changes and small abscesses, in addition to diffuse interstitial fibrosis indicating that the disease was of considerable duration. The lung biopsy specimens reported in the present study were obtained relatively early in the course of the disease and consequently the diffuse interstitial pulmonary fibrosis could be established as the major feature of the disease. The vascular component in the two biopsy specimens was insignificant except in one patient who had received sulfonamide for ten days and then developed urticaria. An allergic element may have been a factor in the vascular changes although it was the impression of the pathologist that the alterations could be ascribed to the coexisting disease. Noteworthy in the case described by Bevans and co-workers[12] and in two by Christie[11] was the finding of localized granulomas in the lung and pleura which had the earmarks of "rheumatoid disease" found in joint lesions. Pleuritis was a feature in all the reported cases.

COMMENTS

A review of the cases reported in the literature and of those here recorded brings out a number of clinical features which, in addition to the pathologic changes previously described, would indicate that the pulmonary, like the joint lesions, of "rheumatoid disease" are part of the same disturbance. Visceral participation in "rheumatoid disease" is usually not recognized clinically; occasionally, it dominates the picture. The attention of the examiner is drawn to obvious articular lesions and, unless the visceral lesions had caused irreversible tissue damage or are demonstrable grossly, they are apt to be overlooked. In fact, this applies also to the postmortem findings. Christie[11] emphasized the fact that only significant active lesions are recognized at autopsy.

The histories of many of the patients indicate an allergic background. Each of the patients described in this paper had some evidence of pre-existing hypersensitivity in the form of urticaria of unknown cause or allergic reaction to sulfonamide or penicillin. The case reported by Katz and Auerbach[13] showed sensitivity to iodide. In the case reported by Bloom and J. H. Rubin[9] the fact that the pulmonary infiltrations appeared at the same time with the rheumatoid symptoms when the pleural fluid had resorbed was suggestive to the authors of an anaphylactic reaction. The same sequence occurred in Case II of the present series. Leys and Swift[8] suspected that the factor of heredity and allergy explained the "rheumatoid disease" in their patient, a boy of ten. Ellman and Ball[7] claim that the visceral and other lesions of "rheumatoid disease" may be explained by hypersensitivity manifestation in tissues. The factor of hypersensitivity in "rheumatoid disease" has been discussed fully in a number of publications by Rich and Gregory[16,17] and need not be reviewed here.

Of particular significance in the cases analyzed in this report was the time relationship between the appearance of symptoms and signs of the "rheumatoid disease" and pulmonary manifestations. In the vast majority the joint symptoms antedated the pulmonary manifestations. In a few the pulmonary symptoms appeared at the time of recrudescence of joint symptoms. On

rare occasion, as in Case III of the present series, acute joint and pulmonary manifestations appeared simultaneously at the onset of the disease. At times a nondescript "pneumonia" or "pleurisy" preceded the joint symptoms for a brief period and with the appearance of swollen, painful joints the pulmonary disease appeared to become reactivated. The later course of events was often characterized by a parallelism in the symptoms referable to both joint and lung lesions.

The chest x-ray findings in "rheumatoid disease" are of major interest since the lung changes portray dynamic phases in the evolution of the process. At times the pulmonary infiltrations are transitory.[8,9] The writer has not encountered any instance of remissions and exacerbations of pulmonary lesions demonstrable roentgenologically, but such occurrences may be expected if chest x-rays are taken frequently, especially during periods of recrudescence of the "rheumatoid disease." The most frequent expression of "rheumatoid disease" in the chest is as a pleuritis manifesting itself in small serous effusions; large collections of fluid are more apt to be associated with anasarca and to be caused by cardiac failure. The frequent elicitation of a pleural friction rub on auscultation during life and the almost inevitable presence of fibrinous or dense pleural adhesions in biopsy or autopsy specimens has been referred to previously.

The chest x-rays in "rheumatoid disease" usually show a bilateral, more or less symmetrical distribution of abnormal lung markings. The case reports, describing at autopsy circumscribed granulomatous lesions in the lungs or pleura, either do not include chest x-ray illustrations or only meager descriptions of the findings. The changes in the lungs are usually discovered accidentally at autopsy. One of the cases described by Christie[11] showed roentgenologically a round, dense shadow 6 cm. in diameter in the right upper lobe. Autopsy revealed it to be a large granuloma with histologic features similar to those found in periarticular nodules of "rheumatoid disease." Once it is recognized that rheumatoid lesions in the lungs may duplicate similar lesions in joints and other parts of the body, the finding of localized disease in chest x-rays will undoubtedly receive greater attention in the future.

The bilateral pulmonary mottlings seen roentgenologically in "rheumatoid disease," as shown in the two lung biopsy specimens and in the autopsy findings described previously, represent interstitial parenchymal changes related to the underlying disease. The infiltrations may be small and evenly distributed, simulating miliary tuberculosis,[9] or they may be of a nodular character affecting chiefly the mid and lower lung fields, simulating sarcoidosis, inhalational dust disease or bronchogenic tuberculosis,[7,8] or they may be irregular, of patchy distribution simulating viral or bacterial bronchopneumonia (Case III of present series). After subsidence of the acute stage of the disease, the markings assume a more linear configuration of a delicate or coarse reticular network such as one sees in lymphangitic carcinomatosis or diffuse interstitial fibrosis of the lungs (Cases I, II and III of present series). In long-standing disease secondary bronchopneumonia and suppuration tend to obscure the basic pattern. There is no characteristic picture characterizing the pulmonary lesions in "rheumatoid disease." But if one views the chest x-ray appearances in the light of the history, physical examination and laboratory findings, one may discern in the film "roentgenologic equivalents" in the sense that the gross and histologic findings offer "morphologic equivalents"[18] of similar conditions.

Other features of "rheumatoid disease" with special reference to pulmonary lesions will be described briefly under several subheadings.

Collagen Diseases and "Rheumatoid Disease." "Rheumatoid disease" is commonly included among the so-called collagen diseases, although some question such a relationship.[19] The collagen diseases constitute a group of disorders showing similar anatomic changes in the way of fibrinoid degeneration of connective tissue, also vascular and serous membrane involvements.[20,21] One of the reasons which has given rise to doubt that "rheumatoid disease" is a member of the collagen group is the fact that disseminated lupus erythematosus, scleroderma, dermatomyositis and polyarteritis nodosa, the more prominent members, are also often accompanied by arthritic, arthralgic and myositic symptoms. By the same token, however, it may be that in certain cases the joint involvement may constitute the major expression of the disease.

Support for the probable existence of a "common denominator"[21] between "rheumatoid disease" and the collagen group is obtained largely from indirect evidence. Cases have been described characterized by such blending of organ involvements,[22–24] including the presence of "rheumatoid disease," as to provide at least

an index of suspicion that the latter is a component member of the collagen group. The results of experimental[16,17] and histopathologic studies,[25–27] as well as the manner of response to hormonal treatment,[28,29] have shown parallel features in one way or another for the majority of the group. But, as emphasized repeatedly by Klemperer,[30] the collective term, "collagen diseases" includes a group of heterogeneous conditions which has in common a systemic alteration of connective tissue. This does not necessarily indicate a common cause. In fact, it would seem that the only incontestable link between the several members of the collagen group is that no cause is known.

"Rheumatoid Disease" and Rheumatic Pneumonia. Although the inclusion of rheumatic pneumonia in this discussion may not seem directly related to the subject, it may be pointed out that the pulmonary lesions of "rheumatoid disease" are not unlike those encountered in rheumatic pneumonia, including the frequent occurrence of pleurisy in both conditions. Some years ago Klinge[31] expressed the belief that rheumatoid arthritis and rheumatic fever are one and the same. Dawson[32] lent further support to this view by finding that the subcutaneous nodules in rheumatic fever and rheumatoid arthritis represent different phases of the same fundamental process. Young and Schwedel[33] found an extremely high incidence of rheumatic heart disease in rheumatoid arthritis, confirming previous pathologic studies.[4] Recently Kersley[34] analyzed the histories of 750 cases of rheumatoid arthritis and found thirty-eight in whom the onset of the disease was so acute as to resemble rheumatic fever. In 10 per cent of the entire group there was a past history of the latter.

Rheumatic pneumonia is an integral part of rheumatic fever, no less than the articular, cardiac and other visceral involvements. Rare instances have been described of patients succumbing in the acute stage of rheumatic fever as a result of pulmonary involvement without significant cardiac involvement.[35] There are also reports of patients who survived the pneumonia and shortly thereafter developed signs of rheumatic carditis. The writer had occasion to follow the course of a girl ten years of age whose pulmonary and cardiac disease progressed simultaneously and rapidly to a fatal issue within a period of seven months. Signs of rheumatic heart disease and chamber enlargement, as well as diffuse infiltrations in both lungs which could not be ascribed to cardiac decompensation, appeared to run a parallel course. Autopsy revealed evidence of advanced valvular heart disease and rheumatic pneumonia.[14]

Noteworthy is the fact that the lung changes in rheumatic pneumonia and virus pneumonia have many features in common, including the presence of a hilar membrane, mononuclear cell infiltration, non-bacterial exudate, capillary engorgement and interstitial edema. It is not improbable, as suspected by some observers, that rheumatic pneumonia may often be mistaken for a virus infection and that at least a small proportion of cases designated virus infection are instances of rheumatic pneumonia without outward manifestations.[35] Muirhead and Haley[37a] report the case of a twenty-five year old white woman who had known healed inactive cardiac lesions and a peculiar interstitial pneumonitis concomitantly. The pneumonitis was widespread, demonstrating a healed proliferative phase with extensive fibrosis and an active exudative phase. In addition, partly healed arterial lesions were observed in the lungs. The authors point out that this case offered an additional point of interest in that the pulmonary lesions resembled in certain respects the changes described by Hamman and Rich[38] in their cases of diffuse interstitial pulmonary fibrosis.

"Rheumatoid Disease" and Diffuse Interstitial Pulmonary Fibrosis. In certain cases of diffuse interstitial pulmonary fibrosis of unknown etiology the disease may be due to failure of resolution with resulting organization of an acute interstitial pneumonia of the type commonly known as primary atypical pneumonia.

Auerbach, Mims and Goodpasture[37b] point out that solution of fibrin has long been held to be a function of enzymes derived from polymorphonuclear leukocytes. Exudates which are rich in fibrin and poor in leukocytes are more apt to organize. These authors suggest that the widespread use of potent antimicrobial agents is contributing to a rising incidence of premature organization of pulmonary exudates with resulting fibrosis of lung tissue. An additional factor may be present in the allergic reactions which often accompany sulfonamide and penicillin treatment. Atypical pneumonias treated with antibiotics are not frequently associated with hypersensitivity reactions. The occasional encounter of diffuse interstitial fibrosis of the lungs in certain collagen, hyperergic and "rheumatoid" disease suggests a related mechanism.

Roentgenologic and pathologic changes in the lungs of such cases are indistinguishable from those found in patients with "rheumatoid disease," and in patients with interstitial pulmonary fibrosis of the type described by Hamman and Rich.[38] The latter draw attention to the fact that Winternitz examined the specimens obtained from their patients and found a striking resemblance to that found in the lungs of animals during experimental investigations on influenzal pneumonia. The lung biopsy specimens of the two cases discussed previously, as well as lung biopsy and autopsy material of a larger group of patients with diffuse interstitial pulmonary fibrosis,[15] were reviewed on various occasions by Zimmerman[39] and the latter expressed a similar opinion.

Hamman and Rich also draw attention in their publication to a group of cases of "current bronchopneumonia of unusual character and undetermined etiology" reported by Kneeland and Smetana[40] in which one of the cases corresponded clinically and anatomically with theirs. In the particular instance, a woman of forty-seven, developed urticaria simultaneously with chills and blood-streaked sputum. The patient was found to have progressive bronchopneumonia which was soon complicated by thrombophlebitis, anemia, hypoproteinemia and right-sided heart failure leading to death. At autopsy lesions were found in the pulmonary arteries suggestive of polyarteritis nodosa, in addition to diffuse interstitial pulmonary lesions characterized by a mononuclear cell exudate and a tendency to organization, also thickening of alveolar septa and narrowing of alveolar spaces. The patient had received sulfapyridine and the vascular changes may have been related to the drug.

Of particular significance is the fact that among the fifty-two patients with atypical bronchopneumonia described by Kneeland and Smetana[40] was a group of six "in whom the clinical picture of a severe and prolonged bronchopneumonia was complicated by a variety of phenomena suggesting that tissues other than pulmonary alone were involved. Among these phenomena were migratory polyarthritis, erythematous skin eruptions, slight enlargement of the spleen and lymph glands, jaundice, gross hematuria, fibrinous pericarditis and encephalitis. All six happened to be females and as these perplexing clinical panoramas unfolded themselves the notion kept recurring that there must be an associated element of diffuse vascular disease of the type seen in disseminated lupus or periarteritis nodosa."

ADDENDUM

Since submitting this article, I have followed the course of a fourth patient with "rheumatoid disease" and diffuse interstitial pulmonary fibrosis. A sixty-five year old woman was admitted to the Medical Division of Montefiore Hospital (Dr. Louis Leiter, Chief) with a history of concurrent onset of joint pains, fever and acute respiratory symptoms diagnosed as pneumonia in another hospital. The disease was of eight months' duration. The chest x-rays and lung biopsy specimen revealed a picture similar to that noted in the cases cited. Noteworthy was the fact that in this case the fine rales heard throughout both lungs, which were ascribed to fibrinous pleurisy, probably originated in the alveolar spaces since the small bronchioles showed no histologic abnormalities while the alveolar spaces showed focal atelectasis. The blood vessels were unremarkable. The specimen showed only minimal thickening of the visceral pleura.

SUMMARY

"Rheumatoid disease" is a more descriptive term than rheumatoid arthritis since the condition affects various parts of the body including the locomotor system. The disease may be associated with pulmonary lesions which are part of the same disturbance. The pulmonary lesions may simulate acute atypical pneumonia, acute rheumatic pneumonia or acute, diffuse interstitial pulmonary fibrosis. In some cases these several manifestations represent one and the same disease.

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Liver Disease in Sickle Cell Anemia*

A Correlation of Clinical, Biochemical, Histologic and Histochemical Observations

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Relatively little has been published regarding liver function in patients with sickle cell anemia.[1] Clinical descriptions occasionally refer to the occurrence of some form of "hepatitis" or "evidence of increasing hepatocellular damage" in this disease.[2,3] In many instances chronic enlargement of the liver has been noted and transient hepatomegaly often occurs during crises. The frequent findings of bilirubinuria and high values for direct-reacting serum bilirubin[4] suggest that hepatic involvement is common. In recent years clinical and laboratory evidence of liver dysfunction in patients with sickle cell anemia has been attributed to viral hepatitis, particularly in those who have received many blood transfusions.[5]

In at least twelve of fifteen patients with sickle cell anemia, Fenichel, Watson and Eirich[6] noted non-specific abnormalities of the electrophoretic pattern for serum proteins similar to those which occur in viral hepatitis and portal cirrhosis. The observations of these authors as well as the findings[7] in two of our patients with sickle cell anemia suggested that at least some of the hepatic dysfunction in this disease might be a manifestation of the sickle cell anemia itself. Therefore, further investigations were undertaken in an attempt to determine the nature of the liver changes associated with this disease. In addition to clinical, biochemical and electrophoretic studies, histologic and histochemical observations were made on liver tissue obtained by needle biopsy from four patients. After these investigations had been started an excellent report on the clinical and biochemical findings in fifty patients and autopsy studies of twenty-one was published by Green, Conley and Berthrong.[8] They concluded that the hepatic disease present in some of their cases seemed to be a specific manifestation of sickle cell anemia and could not be explained on any other basis.

METHODS

Biochemical Determinations. The following biochemical determinations were made: total and direct-reacting serum bilirubins,[9] blood glucose,[10] serum alkaline phosphatase,[11] cephalin-cholesterol flocculation test,[12,13] thymol turbidity test,[14] thymol flocculation test,[15] serum colloidal gold reaction[16] (Boerner reagent[17]), scarlet red test,[18] serum albumin and globulins and total serum proteins,[19] serum amylase[20] and lipase,[21] urine bilirubin[22] and urobilinogen.[23,24] Bromsulfalein retention[25] was also determined. For two patients duplicate determinations of serum fatty acids,[26] phospholipids[27] and total and free serum cholesterol[28] were made in the Research Laboratory, Jefferson Medical College, under the direction of Dr. I. J. Pincus. The cholesterol ester fraction noted in Table I was calculated by subtracting the free from the total cholesterol value. The remaining serum lipid determinations were made at the Graduate Hospital. These included total serum lipids[29] and total serum cholesterol and esterified fraction.[30] The free cholesterol was calculated as the difference between the total and ester values.

As indicated in Table VI, most biochemical determinations for patient no. 4 were made at the Philadelphia General Hospital. These included

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TABLE I

CASE I—LABORATORY DATA*

Date	Hemoglobin	R.B.C.	Retic.	W.B.C.	Serum Bilirubin		Urine		Related to Lipid Metabolism							Related to Protein Metabolism							Serum Alk. Phosphatase	Bromsulfalein Retention %
					Direct	Total	Bile	Urobilinogen	Total Serum Lipids	Serum Phospholipids	Serum Fatty Acids	Serum Cholesterol				Total Serum Proteins Albumin/Globulin	CCF		TT	TF	SCG	SR		
												Total	Free	Ester	Free/Total Ratio		(24 hr.)	(48 hr.)						
Normal	13.0–15.0 gm./100 cc.	4.2–5.4 million/cu. mm.	Up to 1.5%	5–10 thousand/cu. mm.	Up to .4 mg. %	Up to 1.0 mg. %	0	.1 to 1.2 E. units/2 hr.	500–800 mg. %	9–10 mg. % P	7.2–16.2 mEq./L.	150–230 mg. %	50–30% f total	50–70% of total	Up to .5	6.0–8.0 gm. % 4.5–5.0/1.5–3.0 gm. %	0–1+	0–2+	1.0–4.0	0–2+	0–2+	0–2+	1.5–5.0 Bodansky units	Dose-5 mg./kg. body wt. Normal less than 5% in 45 min.
11/30/52	8.5	....	....	36.6	....	....	...	.....	...	..	..	...	...	...	...	.....	...	...	...	...	...	..	....	...
12/1/52	....	....	....	....	9.6	15.2	...	.....	...	..		248	128	120	.52	7.60 3.98/3.62	3+	3+	4.0	3+	0	0	15.8	...
12/2/52	7.4	....	....	....	....	....	...	>12.2	...	..	..	...	...	...	...	.....	...	...	...	...	..	..	...	
12/3/52	6.5	2.5	24.3	36.4	....	....	...	.....	...	..	..	...	...	...	...	.....	...	...	...	...	..	..	....	...
12/4/52	....	....	....	28.0	....	....	...	>5.1	...	..	..	...	...	...	...	.....	...	...	...	...	..	..	....	...
12/5/52	....	....	....	28.0	15.2	19.0	...	....	..	..	..	..	..	..	..	6.88 3.45/3.43	0	0	4.0	0	0	0	17.2	...
12/6/52	13.0	4.4	....	26.2	....	....	...	.....	...	..	..	186	116	70	.62	.....	...	...	...	...	..	..	...	...
12/8/52	10.0	....	....	21.4	8.9	13.2	...	.....	...	..	..	160	70	90	.44	6.40 3.52/2.88	±	+	3.0	0	0	0	12.0	...
12/9/52	9.3	3.3	....	16.5	....	....	...	.....	...	..	..	...	...	...	...	.....								...
12/11/52	11.9	4.0	....	17.4	....	....	...	>5.2	...	...	...	...	...	...	...	.....	...	...					....	...
12/13/52	10.2	....	4.8	15.6	20.8	26.4	...	.....	...	..	..	150	90	60	.60	.....	...	...	...		..	..	8.0	...
12/15/52	14.4	4.75	....	12.5	....	....	...	1.3	...	..	..	...	...	...	...	.....	...	..	...	...				...
12/19/52	....	....	....	....	....	....	...	.....	...	..	..	...	...	...	...	.....	2+	2+	6.0	2+	0	0		...
12/21/52	....	....	....	....	19.0	24.5	...	.....	...	..	..	...	...	...	...	.....	...	...	...	...	..	..	..	...
12/22/52	13.0	4.8	....	10.0	....	....	3+	.....	...	..	..	..	....	...	...	.....	...	...	...	...	...	...		...

TABLE 1 (*Continued*)

Date	Hemoglobin	R.B.C.	Retic.	W.B.C.	Serum Bilirubin		Urine		Related to Lipid Metabolism							Related to Protein Metabolism							Serum Alk. Phosphatase	Bromsulfalein Retention %
					Direct	Total	Bile	Urobilinogen	Total Serum Lipids	Serum Phospholipids	Serum Fatty Acids	Serum Cholesterol				Total Serum Proteins Albumin/Globulin	CCF		TT	TF	SCG	SR		
												Total	Free	Ester	Free/Total Ratio		(24 hr.)	(48 hr.)						
Normal	13.0–15.0 gm./100 cc.	4.2–5.4 million/cu.mm.	Up to 1.5%	5–10 thousand/cu. mm.	Up to .4 mg. %	Up to 1.0 mg. %	0	.1 to 1.2 E. units/2 hr.	500–800 mg. %	9–10 mg. % P	7.2–16.2 mEq./L.	150–230 mg. %	50–30% of total	50–70% of total	Up to .5	6.0–8.0 gm. % 4.5–5.0/1.5–3.0 gm. %	0–1+	0–2+	1.0–4.0	0–2+	0–2+	0–2+	1.5–5.0 Bodansky units	Dose-5 mg./kg. body wt. Normal less than 5% in 45 min.
12/26/52	11.4	4.0	.3	13.0	....	....	...	.....	...	..	..	...	...	...	...	.....	...	...	...	...	..	..	....	...
12/27/52	....	....	....	....	14.6	18.2	...	.....	800	..	..	226	132	94	.59	8.40 4.52/3.88	...	0	3.0	0	0	0	14.0	...
12/29/52	....	....	....	....	....	....	...	.....	...	..	..	...	...	...	...	.....	0	0	3.0	0	0	0	....	...
12/30/52	13.4	4.4	1.2	21.8	....	....	...	1.4	...	..	..	...	...	...	...	.....	...	...	...	...	..	..	....	...
12/31/52	....	....	....	....	....	....	...	.....	656	..	..	...	...	...	...	.....	...	...	...	...	..	..	....	...
1/7/53	12.2	4.4	1.2	13.4	5.3	6.9	...	.....	...	..	..	196	90	106	.46	.....	...	...	...	...	..	..	8.2	...
1/14/53	11.5	4.1	1.2	13.0	3.6	4.8	...	.3	...	..	..	240	146	94	.61	7.36 3.85/3.51	0	0	2.5	0	0	0	....	5.8
1/21/53	....	....	....	....	....	....	...	.....	...	..	..	...	...	...	...	.....	...	...	...	...	..	..	9.8	...
1/22/53	....	....	....	....	2.2	3.2	...	.....	...	..	..	140	72	68	.51	.....	...	...	...	...	..	..	8.6	...
1/27/53	....	....	....	....	2.1	2.9	...	.....	...	..	..	264	124	140	.47	6.40 4.12/2.28	...	...	...	...	..	..	9.0	...
1/31/53	....	....	....	....	....	....	...	.....	...	..	..	264	134	130	.51	.....	...	...	...	...	..	..	....	...
2/3/53	....	....	....	....	1.9	2.5	...	.....	...	..	..	...	...	...	...	.....	...	...	...	...	..	..	....	...
2/4/53	....	....	....	....	1.7	2.6	0	1.8	...	..	..	260	140	120	.54	6.96 3.98/2.98	0	0	2.0	0	0	0	7.4	...
2/5/53	12.8	4.5	....	12.0	....	....	...	.....	...	..	..	...	...	...	...	.....	0	0	1.5	0	0	0	....	...

* Abbreviations—R.B.C.—red blood cells; Retic.—reticulocytes; W.B.C.—white blood cells; CCF—cephalin cholesterol flocculation; TT—thymol turbidity; TF—thymol flocculation; SCG—scarlet colloidal gold; SR—scarlet red.

total and direct-reacting serum bilirubins,[9] total and free serum cholesterol,[31] total serum proteins, albumin and globulins,[32] cephalin-cholesterol flocculation,[12] thymol turbidity[13] and thymol flocculation[14] tests, serum alkaline phosphatase[33] and bromsulphalein retention.[25] Urine bilirubin[24] and twenty-four-hour urinary urobilinogen excretion[34] were determined.

Serum proteins were studied by paper electrophoresis.[35] Electrophoretic analyses of three samples of serum and one of plasma (with heparin added as anticoagulant) were carried out in an Aminco-Stern universal electrophoresis apparatus.* The samples were diluted with barbiturate buffer of ionic strength, 0.1 and pH 8.45 at 21°c. The determinations were made at 2°c. in the standard cell having a cross sectional area of 0.75 sq. cm. The optical system included a cylindrical lens.

Histologic and Histochemical Methods. The technic of liver biopsy and the histologic and histochemical methods employed during this investigation have already been described in detail.[7] The liver tissue obtained by needle biopsy was aspirated into cobalt-formal-calcium solution and fixed in either this or 80 per cent ethanol. Frozen and paraffin sections were prepared as required. For histologic studies the following staining methods were employed: hematoxylin and eosin, a modification of the Mallory stain for connective tissues and a silver technic for reticulin. Histochemical procedures included Oil Red 0 and Sudan Black B for lipids in general, Nile Blue sulfate for the differentiation of acidic and neutral lipids, the acid hematein test for phospholipids and phosphatidic acids, the periodic acid-Schiff's reaction with amylase-treated controls for glycogen, the Feulgen reaction and pyronin-methyl green staining with appropriate enzyme-treated controls for desoxypentose and pentose nucleic acids, respectively, and a modification of Perls' test for iron-containing pigments.

CASE REPORTS

CASE 1. R. G., a twenty-one year old Negress, was admitted to the Graduate Hospital, November 30, 1952, because of lower abdominal pain and jaundice. She stated that on May 4, 1952, she gave birth to a normal child and that because of anemia she had received two blood transfusions before delivery and one after it. About two months later she first noticed that her eyes were jaundiced. There was no associated pain, anorexia, fever or pruritus. Her urine became dark and her stools were brown. The icterus increased progressively; however, she felt well enough to continue her housework. During September, 1952, she began to experience sharp, shooting pains in her arms and legs, across her lower abdomen just above the symphysis pubis and across her lower back. This intermittent pain persisted for about one week and then subsided spontaneously. During the night before admission it returned with greater intensity than previously and was more marked in the lower extremities. This episode persisted for approximately twenty-four hours. Associated with it were malaise, generalized weakness and once, vomiting.

Every few months since childhood she had experienced episodes of sharp, shooting pains in her arms and legs. She had always been thin, felt weak and, compared with her friends, had undue shortness of breath on exertion. There was no history of exposure to hepatotoxic or hemotoxic drugs or of previous jaundice. She drank beer only occasionally. There was no family history of anemia, jaundice or vague chronic illness.

She was 5 feet 4 inches tall, and weighed 110 pounds. Her sclerae were deeply icteric. The retinal veins were tortuous. The heart was normal in size. The blood pressure was 122/65 mm. Hg. Her liver was palpable 2 cm. below the costal margin in the mid-clavicular line on inspiration. Its edge was round and not tender. There were no other relevant, abnormal physical findings.

Her hemoglobin concentration was 8.5 mg. per 100 ml. blood, white cell count 36,600 per cu. mm. with 84 per cent neutrophils. Peripheral blood smear showed many sickle and target cells and 35 normoblasts per 100 white blood cells. Anisocytosis, poikilocytosis, polychromatophilia and Howell-Jolly bodies were noted. A sternal bone marrow smear showed a marked increase of cells, especially normoblasts and pronormoblasts, and a moderate shift to the left of granular leukocytes. A diagnosis of sickle cell anemia in crisis was made. The sickling test was subsequently found positive.

The day following admission only slight arm pain persisted. After this subsided there was no further recurrence of pain. Although malaise

* (Model 5-8000 of the American Instrument Co., Silver Spring, Md.)

and weakness were prominent for the next three days, she was comfortable and her appetite increased slightly. She received a total of 3,500 ml. of blood between December 3rd and December 14th. Her temperature which was 101°F. on November 30th, rose to 105°F. on December 1st, fell to 102°F. for two days and remained elevated at about 100–101°F. until December 13th, following which, with the exception of an occasional rise to 99.6°F., it remained normal.

Because the reticulocyte count had decreased to 4.8 per cent on December 13th and was only 3 per cent nine days later, it was considered that the hemolytic process had largely subsided. She felt much better and ate more of the highly nutritious diet prescribed. Deep icterus persisted. The sedimentation rate (Wintrobe) on December 3rd was 13 mm. per hour. The blood Wassermann and Coombs tests were negative. One and two plus albuminuria accompanied the hemolytic crisis.

The presence of a hyperplastic bone marrow and of marked reticulocytosis in a patient with sickle cell anemia permitted the diagnosis of a hemolytic type of jaundice with certainty. However, it was impossible to attribute the icterus solely to the hemolytic process. The level of serum bilirubin, particularly of the direct-reacting fraction, and the presence of bile in the urine caused consideration to be given to another pathogenetic mechanism for the jaundice. Choledocholithiasis was the only extrahepatic cause given serious consideration. Her recent pregnancy, the known high incidence of cholelithiasis in sickle cell anemia, the high levels of serum alkaline phosphatase and the normal flocculation tests observed during certain phases of her illness lent some support to this hypothesis. An associated intrahepatic rather than posthepatic icterus was favored by such features as the absence of abdominal pain at the onset of icterus, the history of blood transfusions two months before (suggesting viral hepatitis), the absence of pain referable to the biliary tract at any time during her illness and the abnormal cephalin-cholesterol flocculation test on admission. In spite of the high incidence of gallstones in sickle cell anemia, no report of jaundice due to calculous obstruction could be found in the literature. However, Henderson[2] and Green, Conley and Berthrong[8] have each reported one case in which stones were demonstrated in the common duct at autopsy.

The consensus clinically favoured hepatocellular disease rather than extrahepatic obstruction occurring in association with the hemolytic process of the sickle cell anemia crisis.

On December 27th her liver was just palpable at the costal margin on deep inspiration. A needle biopsy was taken at 9:30 A.M. after she had been fasting for twelve hours. Venous blood was withdrawn between 9:05 and 9:20 A.M. The results of some of the laboratory determinations on this specimen and of other studies throughout hospitalization are recorded in Table I. The blood sugar concentration was 99 mg. per cent and the serum amylase and lipase values were 109 mg. per cent and 0.8 ml. N/20 NaOH, respectively. Electrophoretic analysis (Table II) of the plasma revealed that the amount of fibrinogen was reduced. It was probably even less than the value given in the table because the pattern was difficult to interpret in the fibrinogen region. There was a reduction in albumin and an increase in gamma globulin in both serum and plasma.

Microscopic examination of the biopsy specimen (Figs. 1 and 2) revealed disruption of normal liver architecture. There was diffuse, parenchymal cell degeneration, which was more marked in some regions, and areas of necrosis, which varied in size, showed no special zonal distribution and were only sometimes associated with mononuclear cell infiltration. The supporting reticulin of the necrotic areas had collapsed. There was slight mononuclear cell infiltration of portal areas. Bile pigment was found in the parenchymal cells and especially where degeneration and necrosis were prominent. Canalicular bile plugs were common, especially centrilobularly. In addition to the areas of necrosis, focal areas of "atrophy" were also found. The sinusoids were not widened. In some sites ghosts of red blood cells were present in clumps. Kupffer cells were prominent and filled with bile pigment.

She continued to improve and the icterus diminished considerably. On January 21, 1953, cholecystography revealed a cluster of radiopacities of calcific density which were considered to represent biliary calculi in a nonfunctioning gallbladder. There were no radiologic abnormalities in her chest, skull or long bones. The electrocardiogram was compatible with left ventricular hypertrophy.

On February 4th a second liver biopsy was

taken after fifteen hours' fasting. The results of laboratory determinations made on blood drawn five hours before the biopsy are noted in Table I. The serum amylase and lipase values were 126 mg. per cent and 0.7 ml. N/20 NaOH, respectively. She was discharged the day following the biopsy, feeling well but slightly icteric.

TABLE II

RESULTS OF ELECTROPHORETIC ANALYSIS OF SERUM AND PLASMA SAMPLES

Case	Sample and Boundary	Potential Gradient	Per cent of Total Protein						A/G Ratio	Mobility
			Albumin	α_1-Globulin	α_2-Globulin	β-Globulin	Fibrinogen	γ-Globulin		
		v/cm.								
I	Serum: Ascdg.	6.21	45.2	4.14	7.96	15.9	....	26.7	0.81	7.09
	Desdg.		42.3	5.38	8.46	15.0	....	28.8	0.82	6.44
	Plasma: Ascdg.	6.49	43.2	(19.8)[1]		11.2	8.2	17.7	....	6.68
II	Serum: Ascdg.	6.54	32.1	10.51	15.15	3.67	("X" 12.85)[2]	26.9	0.47	6.64
	Desdg.		36.1	7.33	15.2	7.33	("X" 14.15)[2]	19.9	0.56	6.36
III	Serum: Ascdg.	6.49	47.1	5.14	7.5	9.09	("X" 8.7)[2] ("Y" 9.09)[3]	13.05	0.89	6.75
	Desdg.		44.9	5.88	4.2	8.4	("X" 6.73)[2] ("Y" 10.05)[3]	19.03	0.82	6.47
Normal Values										
Serum[4]			56.8 ± 3	7.2 ± 1.2	8.7 ± 1.5	12.8 ± 2.3	.....	14.4 ± 2.4	1.33 ± 0.18	....
Plasma[5]			59.6	6.7	8.8	11.0	4.8	9.1	1.68	....

[1] Value is for α_1- and α_2-globulins together.
[2] "X" represents a component having a mobility intermediate between α_2- and β-globulins.
[3] "Y" represents a component having a mobility intermediate between β- and γ-globulins and may be fibrinogen.
[4] Values are from Reiner, Fenichel and Stern (1950).
[5] Values are from Deutsch and Goodloe (1945).

The lobular architecture was normal in the second biopsy specimen. (Figs. 3 and 4.) The outstanding change was the persistence of several focal lesions of parenchymal cells which had undergone degeneration and disintegration and had pyknotic nuclei. In most of these areas there were small collections of lymphocytes and monocytes. There were other small focal lesions, often mid-zonal, in which there was a "falling out" of cells. There was no portal inflammation. The sinusoids were dilated but no engorgement or clumping of red blood cells was present. Kupffer cells were prominent and contained moderate amounts of iron-containing pigment. There was no increase in connective tissue. The arteries were normal.

The histochemical observations for both biopsy specimens are summarized in Table III. Lipid studies were not made on the first one. Minimal amounts of acidic lipids, however, were found in the second specimen. The cytoplasm of the parenchymal cells was well filled with glycogen in the first but not in the second one. Nuclear glycogen vacuolation was absent. In both specimens the amounts of nuclear desoxypentose nucleic acids but not cytoplasmic pentose nucleic acids appeared to be reduced. Small amounts of hemosiderin were found in the parenchymal cells, especially degenerated ones, and larger amounts in the Kupffer cells.

There were certain clinical features which made it difficult to accept a diagnosis of viral hepatitis. Her icterus had persisted over a period of five months prior to hospitalization. The episodes of pain experienced two months before admission could have been associated with crises of sickle cell anemia and the pain which led to hospitalization most certainly was. Icterus persisted for two months in the hospital, making a total period of seven months of jaundice and, at the time of her discharge from hospital, her serum bilirubin was still elevated. The first liver biopsy findings revealed hepatocellular damage evidenced by areas of parenchymal cell degeneration and necrotic ones which were predominantly focal. These histologic findings are not specific for any disease. The evidences of bile retention, especially bile thrombi in canaliculi, are compatible with obstruction, either extra- or intrahepatic, or parenchymal disease. In the second biopsy, taken about six weeks after the first, focal

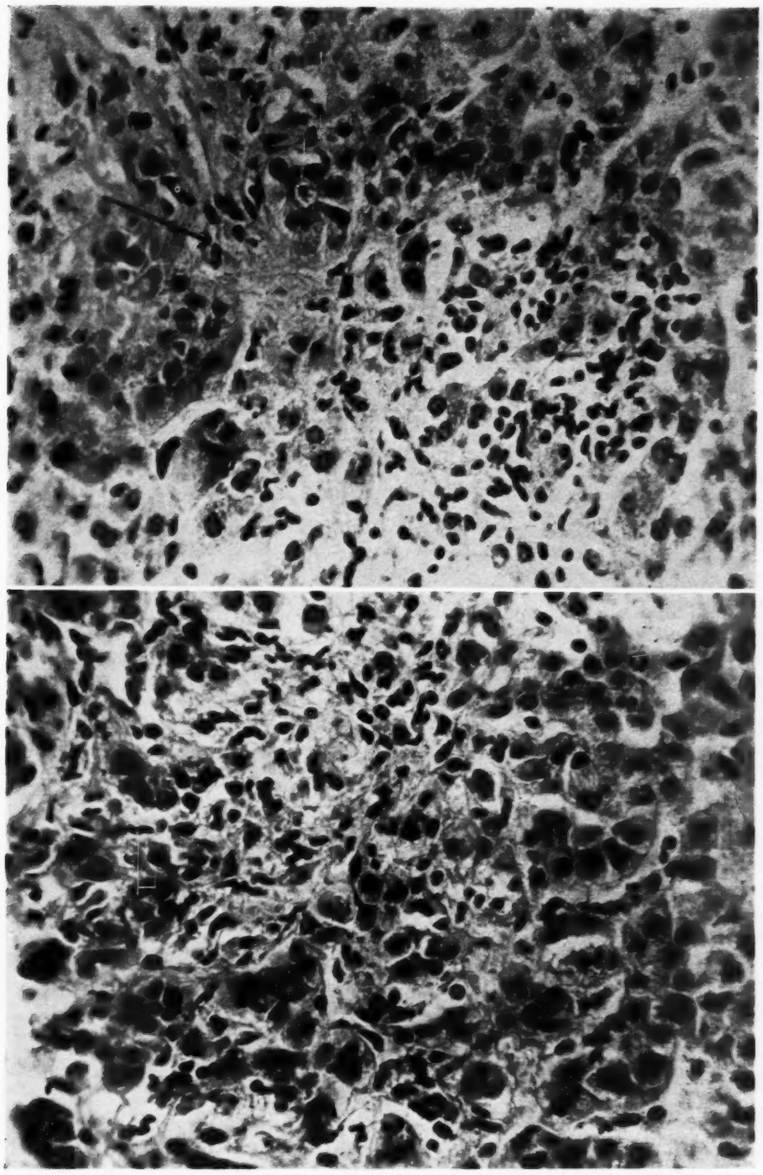


FIG. 1. Patient No. 1; first liver biopsy. At one end of a venous channel there is a small area of parenchymal cell necrosis (arrow). Adjacent to it is a larger area of parenchymal cell necrosis and degeneration associated with mononuclear cell infiltration. Canalicular bile plugs are seen; paraffin section (7 micra); hematoxylin and eosin; × 260.

FIG. 2. Patient No. 1; first liver biopsy showing an area of parenchymal cell necrosis and degeneration with adjacent liver cord disorganization. Canalicular bile plugs are prominent. Paraffin section (7 micra); hematoxylin and eosin; × 260.

parenchymal lesions persisted. If this patient had viral hepatitis associated with her hemolytic jaundice, it would be difficult to know when during her seven-month period of jaundice it played a part unless one is willing to accept that it was present throughout the entire course of her illness. Although impossible to exclude viral hepatitis, it was felt that the hepatic changes were due to some other cause. Drugs, bacterial infections or other agents could not be incriminated. It was considered, therefore, that the hepatic disease might be causally related to the sickle cell anemia itself.

CASE II. R. B., a forty year old Negro was

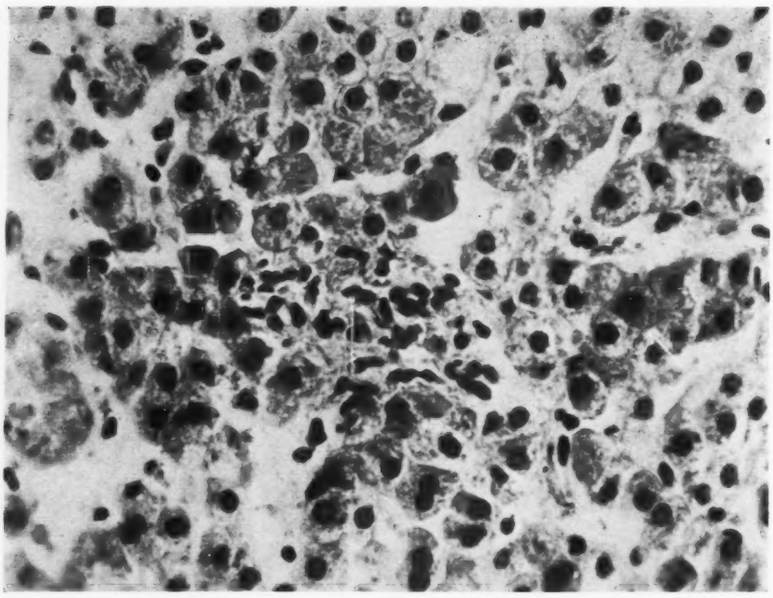


FIG. 3. Patient No. 1; second liver biopsy. A focal lesion consisting of degenerating and necrotic parenchymal cells with mononuclear cell infiltration. There is dilatation of sinusoids and Kupffer cell prominence. Paraffin section (7 micra); hematoxylin and eosin; × 260.

TABLE III

LIVER BIOPSIES—HISTOCHEMICAL OBSERVATIONS[1]

Case		Lipids[2]		Glycogen[3]		Nucleic Acids[4]		Iron Pigment	
		Cytoplasmic Droplets	Cysts	Cytoplasmic	Nuclear (%)	Nucl. D.N.A.	Cyto. P.N.A.	Parenchymal Cells	Kupffer Cells
I	12/27/52	.....	..	4 unif.	0	1	4	1	3
	2/4/53	*tr.*, v. sm., occas. lg., ac., centr.	0	2½ unif.	0	1	3	*tr.*	3
II		*v.f. tr.*, sm., neut., scat.	0	3½ unif.	0–20	1	3	3	3
III*		(0)	(0)	(3)	(0)	(1)	(3)	(4)	(3)
IV		0	0	3 unif.	1	..	3	>4	>4

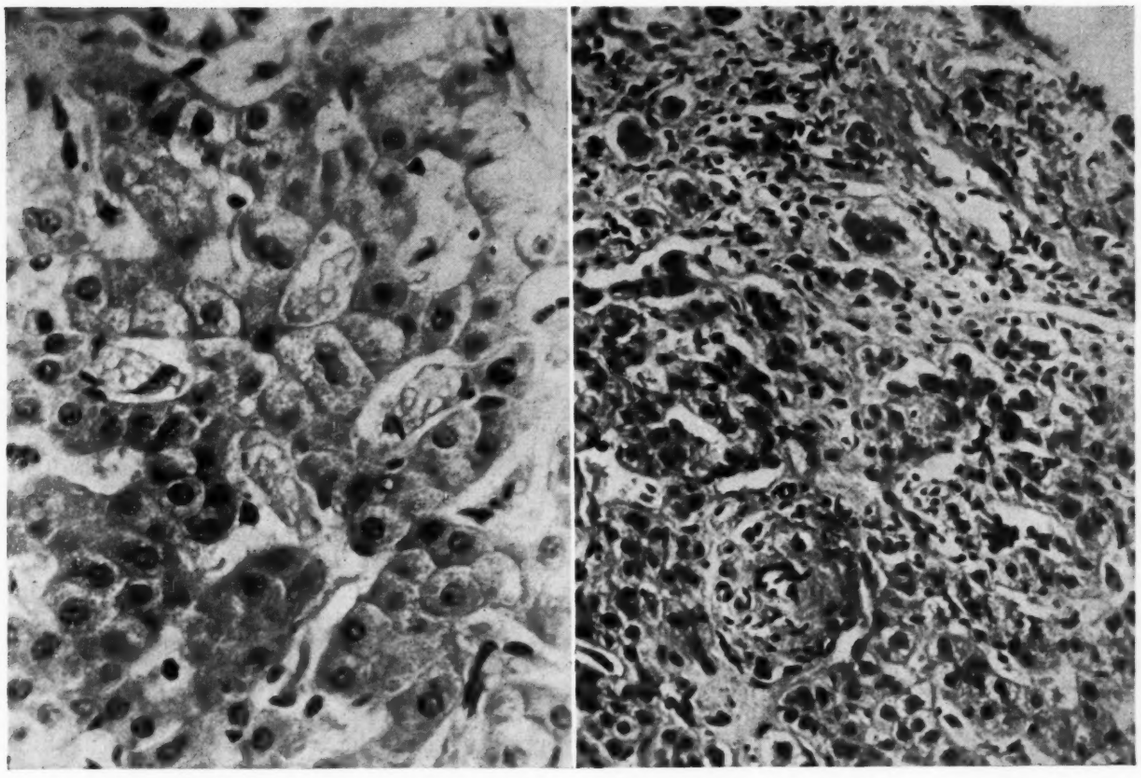
[1] Grading of observations for lipids, glycogen, nucleic acids and iron pigment, ranges from 0 to 4 and includes within the interval 0–1, v.f. tr. (very faint trace), f. tr. (faint trace) and tr. (trace).

[2] Lipids: Separate data are given for cytoplasmic fat droplets and for fatty cysts as follows:
Size: v.sm.—very small; sm.—small; lg.—large
Reaction: ac.—acidic; neut.—neutral
Distribution within hepatic lobules: centr.—central; scat.—scattered

[3] Glycogen: Cytoplasmic: Distribution: unif.—uniform; Nuclear: Percentage of nuclei containing some glycogen.

[4] Nucl. D.N.A.—Nuclear desoxypentose nucleic acid.
Cyto. P.N.A.—Cytoplasmic pentose nucleic acid.

* Little tissue present making the histochemical observations, in parentheses, of limited value.



4 5

FIG. 4. Patient No. 2; first liver biopsy showing clumps of erythrocytes in widened sinusoids. Some of the red cell clumps are bordered by nuclei of Kupffer cells which are prominent. Paraffin section (7 micra); hematoxylin and eosin; × 420.

FIG. 5. Patient No. 2; second liver biopsy. There are bands of cellular connective tissue and adjacent degenerated parenchymal cells. An arteriole with marked narrowing of the lumen is seen in the left lower corner. Paraffin section (7 micra); hematoxylin and eosin; × 110.

admitted to the Graduate Hospital on March 1, 1948, because of episodes of dull, non-radiating, mid-epigastric pain lasting two to three days a week, of one year's duration. The pain usually occurred one or two hours after breakfast and the noon meal, and was associated with nausea, vomiting and generalized weakness. There were no alleviating or aggravating factors. In September, 1947, the pain increased in frequency until it occurred daily. Nausea and vomiting disappeared. He had noticed intermittent scleral icterus since 1946 and it had become constant three or four months prior to admission. There was no fever or pruritus. His stools were brown and, since June, 1947, the urine had been darker than previously. Despite a good appetite, he had lost 20 pounds in weight during the year before admission. No other abnormalities were elicited on systemic review. There was no history of alcoholism.

Examination revealed a 5 foot 6 inch tall, moderately well nourished, gracile male. His sclerae were icteric. The retinal veins were quite tortuous. The heart was enlarged to the anterior axillary line in the sixth interspace. There was a grade 3 systolic murmur at the apex. The blood pressure was 120/80 mm. Hg. His liver was palpable in the mid-clavicular line about four finger breadths below the right costal margin. There was a small superficial pretibial ulcer on his left leg. No other abnormalities on physical examination were found.

The hemoglobin was 8.0 gm., the red cell count was 2,040,000 per cu. mm., reticulocytes 2.6 per cent, white cell count 8,300 per cu. mm. Sickling, polychromatophilia and nucleated erythrocytes were noted in the smear of peripheral blood. A diagnosis of sickle cell anemia was made. There were many sickled erythrocytes and markedly active normoblastic erythropoiesis in the bone marrow. The direct Van den Bergh reaction was 1.68 mg. per cent and the

total, 3.3 mg. per cent. The blood Wassermann was negative, serum amylase 30 mg. per cent and serum lipase, 0.1 ml. N/20 NaOH. The results of other laboratory tests on this and subsequent admissions are given in Table IV. Radio-opacities 2 mm. in diameter were scattered throughout both lung fields; there was a moderate degree of left ventricular enlargement and slight prominence of the pulmonary conus sector. The trabecular pattern of the vertebral bodies was coarser than normal. A markedly deformed duodenal cap with a constant fleck in the mid-portion was interpreted as an active ulcer. Cholecystography and x-rays of the skull and long bones were normal. The electrocardiogram showed non-specific T wave changes. Gastric analysis following an Ewald test meal showed 22 units free acid at seventy-five minutes.

On March 3, 1948, chills and fever to 104.8°F. followed the administration of 500 ml. of blood. Following medical management, the duodenal ulcer healed radiologically. He was discharged on April 19, 1948.

On February 27, 1950, he was readmitted for blood transfusions. He had had only a mild exacerbation of epigastric pain in June, 1949. The findings on examination were similar to those on the previous admission except that his liver could not be palpated in spite of radiologic evidence of moderate hepatomegaly. The blood pressure was 112/70 mm. Hg. Seven 500-ml. blood transfusions were given. The PPD test no. 1 was positive and the histoplasmin test negative. He was given a bland diet. A liver biopsy was taken after he had been fasting for approximately twelve hours. He was discharged on March 15, 1950.

Some of the histologic findings are illustrated in Figure 4. There was marked sinusoidal widening which caused the liver cords to appear prominent. There were clumps of erythrocytes in sinusoids and some were engulfed in Kupffer cells. Except for very occasional, small focal lesions in which liver cells appeared to be atrophic or to have "fallen out," the parenchymal cells were normal. There was slight periarterial thickening. Very little pigment, probably hemosiderin, was present in Kupffer cells and in some parenchymal cells. However, no studies with special stains were made. Some nuclear "ballooning," suggestive of glycogen vacuolation, was present. There was no increase in fibrous tissue.

On February 2, 1953, he was readmitted for blood transfusions. Since discharge in March, 1950, he received a total of 8,000 ml. of blood because of anemia. There had been one recurrence of duodenal ulcer in the interim. On one occasion the liver could no longer be palpated. On this admission he was asymptomatic and weighed 120 pounds (17 per cent underweight). The blood pressure was 124/78 mm. Hg. The liver was grossly enlarged, extending to 10 cm. below the right costal margin in the mid-clavicular line and 8 cm. below the level of the xiphoid. Its edge was round, firm and not tender. Its surface was smooth. Physical findings were otherwise unchanged. A coarsened trabecular pattern at the distal end of the humerus and at the proximal end of the ulna were demonstrated radiologically. He received the routine ward diet. On February 5th a needle biopsy of his liver was taken at 10:40 A.M. after he had been fasting for approximately twelve hours. Venous blood was withdrawn at 9:36–10:40 A.M. The results of the biochemical studies are recorded in Table IV. Other determinations performed on the same blood sample included serum amylase and lipase which were 89 mg. per cent and 0.4 ml. N/20 NaOH, respectively. Qualitative paper electrophoretic studies of the serum from this patient did not reveal any abnormalities; however, electrophoretic analysis showed a reduction in the albumin and beta-globulins. (Table II.) A new component ("X"), between the $alpha_2$- and beta-globulins, was present in considerable amount. He was discharged on February 12, 1953.

Microscopic examination of the biopsy specimen revealed several interesting findings. (Figs. 5 and 6.) There were cellular connective tissue scars in areas without distinct distribution and an increase in periportal connective tissue. The parenchymal cells adjacent to the fibrous tissue were degenerated. The cytoplasm of many parenchymal cells appeared coarsely granular and some contained bile pigment. As shown in Figure 6, there were some focal areas of degenerated hemosiderin laden parenchymal cells. There were also occasional small focal areas of liver cell degeneration and focal areas where liver cells appeared to be undergoing resorption. The walls of some of the arteries were thickened and this change involved adventitial and intimal regions. The lumen of one vessel shown in Figure 5 was considerably narrowed. The sinusoids were dilated and contained some clumps of red

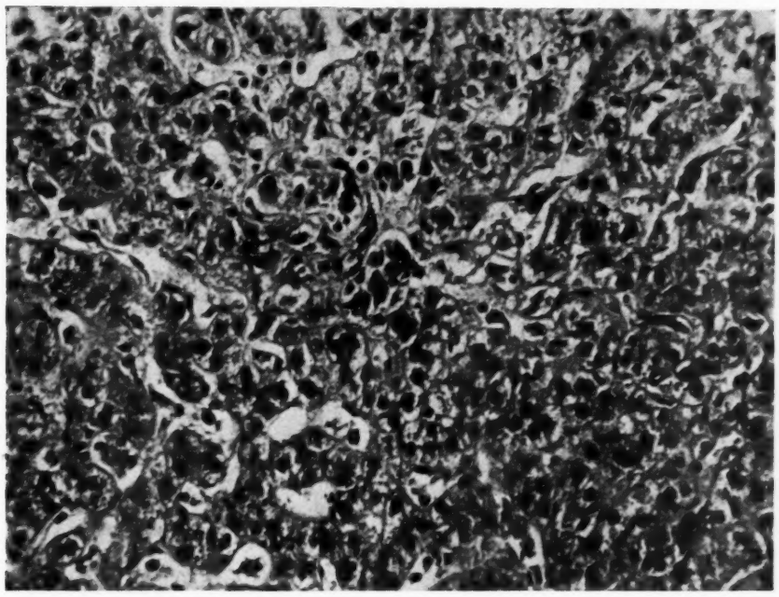


FIG. 6. Patient No. 2; second liver biopsy. In the center of the photograph is a small focal area of degenerated hemosiderin-laden parenchymal cells. The remainder show marked granularity due to hemosiderin. Paraffin section (7 micra); hematoxylin and eosin; × 110.

blood cells. The Kupffer cells were more prominent than in the first specimen and were filled with iron-containing pigment. Occasionally, they bordered the red blood cell clumps. The most significant change was the slight but definite presence of portal cirrhosis.

The histochemical observations on the second biopsy specimen are recorded in Table III. Very faint traces of neutral lipids were found in some of the parenchymal cells all of which contained large amounts of glycogen. Considerable variations in the incidence of nuclear glycogen vacuolation was noted. There might have been some reduction in the amount of nuclear desoxypentose nucleic acids but not in the cytoplasmic pentose nucleic acids. There were moderate amounts of hemosiderin in both the parenchymal and Kupffer cells but not in connective tissue scars. Some bile pigments were present in parenchymal cells.

CASE III. G. L., a fifty-one year old Negro, was admitted to the Philadelphia General Hospital on February 28, 1952. He had been "weak and sickly" all his life but had no serious illnesses until January 30, 1952, when he was admitted to a hospital in an unconscious state. He was discharged on February 19, 1952, with a diagnosis of glomerulonephritis. On the day before admission to the Philadelphia General Hospital he remained in bed because of weakness. About six hours after admission he developed a severe headache and shortly thereafter became semi-comatose. There was no history of alcoholism.

He was lethargic, confused and barely coherent. His temperature was 98.6°F., pulse rate 80 per minute and blood pressure 220/110 mm. Hg. There was grade 2 hypertensive retinopathy. The apex beat was in the fifth interspace, 11.5 cm. to the left of the mid-sternal line. There was a grade 2 apical systolic murmur. His liver was palpable one fingerbreadth below the costal margin in the right mid-clavicular line. There was weakness of the left leg and arm, and with the exception of the right upper abdominal reflex, the cremasteric and abdominal reflexes could not be elicited. The remainder of the examination was normal. His spinal fluid was clear and had a pressure of 220 mm. water.

The weakness of the left arm and leg cleared in twenty-four hours and the confusion in approximately one week. Two days after admission considerable itching of his skin developed. At this time the sclerae were noted to be icteric.

His hemoglobin was 8.1 gm., white blood cell count 8,600 per cu. mm., reticulocytes 5.1 per cent and there was positive sickling on the peripheral blood smear. There was three plus albuminuria, 5 to 7 leukocytes and 3 to 5

TABLE IV

CASE II—LABORATORY DATA*

Date	Hemoglobin	R.B.C.	Retic.	W.B.C.	Serum Bilirubin		Urine		Related to Lipid Metabolism‡							Related to Protein Metabolism							Serum Alk. Phosphatase	Brom sulfalein Retention %
					Direct†	Total	Bile	Urobilinogen	Total Serum Lipids	Serum Phospholipids	Serum Fatty Acids	Serum Cholesterol				Total Serum Proteins Albumin/Globulin	CCF		TT	TF	SCG	SR		
												Total	Free	Ester	Free/Total Ratio		(24 hr.)	(48 hr.)						
Normal	13.0–15.0 gm./100 cc.	4.2–5.4 million/cu. mm.	Up to 1.5%	5–10 thousand/cu. mm.	Up to .4 mg.	Up to 1.0 mg. %	0	.1 to 1.2 E. units/2 hr. (up to 1/20)	500–800 mg. %	(9–10 mg. % P)	(7.2–16.2 mEq./L.)	150–230 mg. % (150–250 mg. %)	50–30% of total (up to 30% of total)	50–70% of total (70% of total)	Up to .5 (up to .3)	6.0–8.0 gm. % 4.5–5.0/1.5–3.0 gm. %	0–1+	0–2+	1.0–4.0	0–2+	0–2+	0–2+	1.5–5.0 Bodansky units	Dose—5 mg./kg. body wt. Normal less than 5% in 45 min.
3/2/48	8.0	2.9	....	8.3	.....	...	...	.....	...	.....	.....	272	128	144	.44	.....	0	0	1.0	0	0	0	7.3	15.3
3/4/48	8.5	3.1	2.6	....	.....	...	...	.....	...	.....	.....	....	...	...	...	.....	...	...	...	..	..	...	.....	....
3/5/48	....	...	....	....	.....	...	0	(1/300)	...	.....	.....	218	100	118	.46	.....	...	...	...	..	..	...	.....	....
3/6/48	....	...	....	....	.....	...	...	.....	...	.....	.....	....	...	...	...	.....	0	0	1.0	0	0	0	16.7	17.5
3/16/48	7.5	2.8	....	....	.....	...	...	.....	...	.....	.....	....	...	...	...	.....	...	...	...	..	..	...	4.32	....
3/22/48	....	...	....	....	.....	...	...	.....	...	.....	.....	....	...	...	...	7.36 3.59/3.77	...	...	...	..	..	...	.....	....
3/29/48	....	...	....	....	.....	...	...	.....	...	.....	.....	....	...	...	...	7.04 3.12/3.92	...	...	...	..	..	...	.....	....
4/5/48	....	...	....	....	.....	...	...	(1/30)	...	.....	.....	....	...	...	...	.....	...	...	...	..	..	...	.....	....
4/6/48	....	...	....	....	Immed.	1.5	...	.....	...	.....	.....	....	...	...	...	.....	...	...	...	..	..	...	.....	....
4/8/48	....	...	....	....	Immed.	3.0	...	.....	...	.....	.....	....	...	...	...	6.96 3.85/3.11	...	...	...	..	..	...	.....	....
2/28/50	6.5	...	8.6	6.8	2.8	5.1	...	(1/40)	...	.....	.....	....	...	...	...	6.00 2.99/3.01 *	...	...	...	..	..	...	.....	19.8
3/2/50	....	...	....	....	.....	...	...	.....	...	.....	.....	....	...	...	...	.....	0	0	1.0	0	0	1+	.....	....
3/6/50	10.5	...	....	5.9	del.	2.0	...	.....	...	.....	.....	258	66	192	.26	6.54 3.65/2.89	...	...	...	..	..	...	.....	16.4
3/7/50	....	...	....	....	2.4	3.5	...	(1/20)	...	.....	.....	....	...	...	...	.....	...	...	...	..	..	...	.....	....

TABLE IV (*Continued*)

Date	Hemoglobin	R.B.C.	Retic.	W.B.C.	Serum Bilirubin		Urine		Related to Lipid Metabolism‡							Related to Protein Metabolism							Serum Alk. Phosphatase	Bromsulfalein Retention %
					Direct†	Total	Bile	Urobilinogen	Total Serum Lipids	Serum Phospholipids	Serum Fatty Acids	Serum Cholesterol				Total Serum Proteins Albumin/Globulin	CCF		TT	TF	SCG	SR		
												Total	Free	Ester	Free/Total Ratio		(24 hr.)	(48 hr.)						
Normal	13.0–15.0 gm./100 cc.	4.2–5.4 million/cu. mm.	Up to 1.5%	5–10 thousand/cu. mm.	Up to .4 mg.	Up to 1.0 mg. %	0	.1 to 1.2 E. units/2 hr. (up to 1/20)	500–800 mg. %	(9–10 mg. % P)	(7.2–16.2 mEq./L.)	150–230 mg. % (150–250 mg. %)	50–30% of total (up to 30% of total)	50–70% of total (70% of total)	Up to .5 (up to .3)	6.0–8.0 gm. % 4.5–5.0/1.5–3.0 gm. %	0–1+	0–2+	1.0–4.0	0–2+	0–2+	0–2+	1.5–5.0 Bodansky units	Dose—5 mg./kg body wt. Normal less than 5% in 45 min.
3/8/50	....	...	....	....	.....	...	...	.....	...	.....	.....	....	...	...	...	.....	...	...	...	..	..	...	2.2	....
3/9/50	11.0	...	....	....	.....	...	...	.....	...	.....	.....	....	...	...	...	.....	2+	2+	1.0	0	0	0	.....	....
5/17/50	9.5	3.6	3.6	10.8	Immed.	2.0	...	.....	...	.....	.....	....	...	...	...	5.84 2.86/2.98	...	...	...	..	..	...	6.0	....
5/19/50	11.0	3.8	....	5.5	.....	...	...	.....	...	.....	.....	....	...	...	...	.....	0	0	1.0	0	0	0	.....	....
7/26/50	5.0	2.5	8.0	6.2	.....	...	...	.....	...	.....	.....	....	...	...	...	.....	...	...	...	..	..	...	.....	....
4/16/52	7.9	2.3	13.2	9.4	2.4	4.3	...	.....	...	.....	.....	....	...	...	...	6.08 3.25/2.83	0	0	1.0	0	0	0	25.6	30.0
2/3/53	6.6	2.7	....	6.5	.....	...	1+	5.6	...	.....	.....	....	...	...	...	.....	...	...	...	..	..	...	.....	....
2/4/53	7.8	2.6	5.3	....	.....	...	1+	.....	692	.....	.....	250	116	134	.47	5.6 3.05/2.55	...	...	...	..	..	...	.....	....
2/5/53	....	...	....	....	2.3	3.8	0	(1/20)	840	(23.9)	(15.3)	(325)	(87)	(238)	(.27)	5.84 3.52/2.32	0	0	1.0	0	0	0	29.0	....
2/7/53	9.8	3.3	....	....	2.3	4.3	±	.....	...	.....	.....	....	...	...	...	.....	0	0	1.0	0	0	0	23.6	....

* Abbreviations: R.B.C.—red blood cells; Retic.—reticulocytes; W.B.C.—white blood cells; CCF—cephalin cholesterol flocculation; TT—thymol turbidity; TF—thymol flocculation; SCG—scarlet colloidal gold; SR—scarlet red.

† In some instances the direct reacting serum bilirubin was determined qualitatively, del.—delayed; immed.—immediate; neg.—negative.

‡ Determinations indicated by parentheses in tests "Related To Lipid Metabolism" were performed in the laboratory of Dr. I. J. Pincus, Jefferson Medical College.

hyaline casts per high power field. The concentration test revealed a fixed specific gravity of 1.010. Phenolsulfonthalein excretion was 5 per cent in fifteen minutes. The blood urea nitrogen was 31 mg. per cent and the Wassermann test was negative. X-ray studies showed a prominent left ventricle. He was discharged on March 21, 1952, with a diagnosis of hypertensive encephalopathy, chronic pyelonephritis, anemia due to toxic suppression of the bone marrow and a sickling tendency.

In June, 1952, he was readmitted because of jaundice and pruritus. For the preceding two months he had experienced episodes of severe, colicky, right upper quadrant pain which, during the past three weeks, had been referred to the right subscapular region. No alleviating or aggravating factors were observed. There was an intolerance of fried and fatty foods. For the previous two weeks there had been pruritus, light brown stools and dark urine, and anorexia for one week. He gave a history of angina of effort, and for the preceding two weeks had noticed swelling of his feet and abdomen.

The physical findings were the same as those on the earlier examination except that his blood pressure was 145/70 mm. Hg and his neck veins were distended. The liver was palpable two to three fingerbreadths below the costal margin in the right mid-clavicular line. Its edge was firm and smooth. There was moderate ankle edema. The stools were light brown. His hemoglobin was 5.6 gm. and there were sickled and nucleated erythrocytes on the peripheral blood smear. A diagnosis of sickle cell anemia was made. Renal function studies were similar to those on the previous admission. The electrocardiogram was compatible with a diagnosis of left ventricular strain secondary to hypertension. A flat film of the abdomen revealed numerous calcified stones in the gallbladder region. During this admission there were several episodes of diffuse abdominal pain which were each of approximately twenty minutes' duration, unaccompanied by other symptoms and relieved by oxygen. He was given three blood transfusions and discharged September 3, 1952. Some of the more relevant laboratory findings during this and subsequent admissions and outpatient visits are recorded in Table v.

Several weeks after discharge, he felt progressively weaker, had frequent nose bleeds, and there was an occasional recurrence of the abdominal pains previously experienced. Ankle edema persisted. During the next few months there was persistent icterus with total serum bilirubin values ranging from 3.71 to 5.97 mg. per cent. The hemoglobin varied from 6.3 to 7.9 gm.

On December 1, 1952, he was readmitted because of dyspnea on slight effort, frontal headaches and ocular pain with blurring of vision. His appetite and dietary intake had been poor for one month and he had vomited two or three times weekly during the preceding three weeks. The vomitus did not contain blood. His stools were black but contained no frank blood. He was listless and lethargic but in no acute distress. He was 5 feet 4 inches tall and weighed 107 pounds. His sclerae were icteric. There was some distention of the neck veins. The tender liver edge was palpable two fingerbreadths below his costal margin in the right mid-clavicular line. The remainder of the physical findings were the same as on previous examinations. Radiologically, his stomach and duodenum were normal. The gallbladder could not be visualized by cholecystography but there were numerous, faceted, calcific stones in the gallbladder area. In view of the history and x-ray findings he was considered for cholecystectomy but rejected because of the serious operative risk. It was difficult to be certain whether hepatocellular disease or choledocholithiasis was present in addition to the hemolytic jaundice.

On February 23rd, the liver was three fingerbreadths below the costal margin in the mid-clavicular line and four fingerbreadths below the xiphoid process. Its edge was sharp, round, smooth and moderately tender. The spleen was not palpable. There was no jugular venous distention. A liver biopsy was performed at 8:55 A.M. after he had been fasting for twenty hours. Venous blood was withdrawn for tests between 8:44 and 8:58 A.M. A very small specimen of liver tissue was obtained which did not permit adequate histologic interpretation. Paper electrophoretic studies of serum proteins revealed no abnormalities. The results of electrophoresis by the Tiselius method are recorded in Table II. The amount of albumin was somewhat reduced. The new component noted in the serum of the patient in Case II was also present but in smaller amount. There might also be a small amount of fibrinogen present. The serum amylase level was 211 mg. per cent and serum lipase 1.1 ml. N/20 NaOH.

On March 5, 1953, he experienced an attack

of severe, sharp bilateral abdominal pain below his umbilicus. Peristalsis was hyperactive. There was no rigidity or guarding. For the following two weeks he had clay-colored stools. On March 25, 1953, the findings on examination of his liver were the same as at the time of the first biopsy. A second biopsy was performed at 8:45 A.M. after he had been fasting for approximately fifteen hours. Again, only a small specimen was obtained. Blood for laboratory tests, the results of which are recorded in Table V, was taken between 8:43 and 8:53 A.M. The blood sugar concentration was 81 mg. per cent.

The striking change on microscopic examination of the specimens obtained at both biopsies was the presence of abnormal amounts of fibrous tissue. (Fig. 7.) There was not enough tissue to determine the type of cirrhosis with certainty but the distribution of the connective tissue favored portal cirrhosis. In the parenchymal and Kupffer cells there were large deposits of pigment which gave a positive reaction for iron. Hemosiderin was also present in the fibrous tissue. There was only a little parenchymal cell degeneration and the involved cells were adjacent to the connective tissue. No apparent, striking pathogenetic relationship between degenerating iron-laden parenchymal cells and the formation of fibrous tissue was present as in Case IV. The sinusoids were widely dilated. In some areas they were filled with clumped red blood cell masses. A large area of parenchymal cell necrosis was found adjacent to an area where the engorgement of sinusoids by clumps of red blood cells was marked. (Fig. 8.) Kupffer cells were only slightly prominent.

Histochemical observations performed on the tissue obtained at the first biopsy are recorded in Table III. Because of the meager amount of tissue upon which these are based they are of little real value. The cytoplasm of the few cells which could be studied contained moderate amounts of glycogen. No nuclear vacuolation was noted. Nuclear desoxypentose nucleic acids but not cytoplasmic pentose nucleic acids may have been reduced in amount.

CASE IV. E. G., a twenty-five year old Negress, was first admitted to the Graduate Hospital, April 12, 1949. During the preceding evening she began to experience a dull, constant throbbing, pain in the left upper quadrant of the abdomen. This increased in severity, spread over the entire abdomen, then gradually subsided on the morning of admission. Residual discomfort remained in the right upper quadrant for a few days, accentuated by motion. Enquiry and subsequent reports from other hospitals revealed that at the age of two years a moderately severe anemia and sickling of her red blood cells had been discovered. She received blood transfusions for anemia at the age of eleven years. Splenomegaly was discovered at this time. When she was twelve years old she was observed in a crisis of sickle cell anemia with generalized pains, fever to 103°F. and marked anemia. From the age of twelve to nineteen years she had twenty hospital admissions, mostly for blood transfusions. Hematologic studies at the age of nineteen years showed that the hemoglobin was 5.4 gm., red cell count 1,330,000 per cu. mm., white cell count 15,000 per cu. mm. and the presence of marked red blood cell sickling.

Intermittent throbbing pains of short duration in varying parts of her body as well as episodes of scleral icterus had been recurring for as long as she could remember. Climbing one flight of stairs resulted in weakness and some dyspnea. Ankle edema had been present nightly for about five years.

Her past history included an illness diagnosed as rheumatic fever at the age of five years with swollen, tender joints of the fingers, wrists and knees. One brother was receiving care for sickle cell anemia in this hospital.

She was well developed and well nourished, alert, cooperative and in only mild discomfort. Her temperature was 101°F., pulse rate 102 per minute, blood pressure 120/70 mm. Hg. The apex beat was palpable in the anterior axillary line in the fifth left interspace. There was a grade 3 shrill, blowing systolic murmur at the aortic area and a grade 1 systolic murmur at the apex. Generalized guarding and tenderness of the abdomen, especially in the right lower quadrant, was present. Rebound tenderness was moderate and generalized and peristalsis was hypoactive. Apart from venous congestion of the retinal vessels, there were no other findings on examination. The hemoglobin was 6.0 gm., red blood cell count 2,040,000 per cu. mm., and reticulocytes 15.1 per cent. The blood smear revealed marked erythrocyte sickling, polychromatophilia, nucleated red blood cells and Howell-Jolly bodies. A diagnosis of sickle cell anemia in crisis was made. During the next two days her symptoms and fever subsided. A plain film of the abdomen showed evidence of slight hepatomegaly. An x-ray of the chest revealed

TABLE V

CASE III—LABORATORY DATA*

Date	Hemoglobin	Hematocrit	Retic.	W.B.C.	Serum Bilirubin		Urine		Related to Lipid Metabolism**							Related to Protein Metabolism							Serum Alk. Phosphatase	Bromsulfalein Retention (%)
					Direct	Total	Bile	Urobilinogen	Total Serum Lipids	Serum Phospholipids	Serum Fatty Acids	Serum Cholesterol				Total Serum Proteins Albumin/Globulin	CCF		TT	TF	SCG	SR		
												Total	Free	Ester	Free/Total Ratio		(24 hr.)	(48 hr.)						
Normal	14.5–15.3 gm./100 cc.	47 cc./100 cc.	Up to 1.5%	5–10 thousand/cu. mm.	Up to .4 mg. %†	Up to 1.0 mg. %	0	0–4.0 E. units /24 hr.	500–800 mg. %†	(9–10 mg. % P)	(7.2–16.2 mEq./L.)	110–300 mg. % (150–250 mg. %)	20–40% of total (up to 30% of total)	60–80% of total (70% of total)	Up to .4 (up to .3)	6.3–8.0 gm. % 4.0–5.5/1.3–3.4 gm. % 6.0–8.0 gm. %† 4.5–5.0/1.5–3.0 gm. %	0–1+†	2+ 2+†	1.0–4.0 1.0–4.0†	0–2+ 0–2+†	0–2+†	0–2+†	1.5–4.5 Shin. units 1.5–5.0 Bod. units†	Dose—5 mg./kg. body wt. Normal less than 5% in 45 min.
2/29/52	8.1	..	...	8.6	....	.....	..	.....	....	.....	.....	.....	....	....	....	.....	....	....	....	...	..	..	....	....
3/3/52	...	..	...	...	....	.85	..	.....	....	.....	.....	.....	....	....	....	.....	....	0	2.5	0	..	..	....	....
3/7/52	9.6	28	5.1	...	....	.....	..	.....	....	.....	.....	.....	....	....	....	.....	....	....	....	...	..	..	....	....
6/12/52	5.6	..	...	9.0	....	10.6	0	.....	....	.....	.....	167	102	65	.60	7.0 3.4/3.6	....	4+	5.7	3+	..	..	5.45	....
6/19/52	...	..	...	...	....	2.8	..	6.53	....	.....	.....	.....	....	....	....	.....	....	....	....	...	..	..	....	....
7/5/52	...	..	...	...	....	3.1	..	4.29	....	.....	.....	.....	....	....	....	.....	....	....	....	...	..	..	....	....
8/21/52	...	..	...	...	....	3.4	..	.....	....	.....	.....	.....	....	....	....	.....	....	2+	1.5	1+	..	..	....	....
12/1/52	4.7	..	...	...	....	.....	..	.....	....	.....	.....	.....	....	....	....	.....	....	....	....	...	..	..	....	....
12/4/52	7.4	..	...	...	....	5.3	..	.....	....	.....	.....	.....	....	....	....	.....	....	....	....	...	..	..	....	....
12/15/52	6.0	..	...	...	....	2.8	..	.....	....	.....	.....	.....	....	....	....	.....	....	0	1.6	1+	..	..	....	....
12/17/52	...	..	...	...	....	.....	0	0	....	.....	.....	.....	....	....	....	.....	....	....	....	...	..	..	....	....
12/18/52	...	..	...	...	....	.....	..	1.24	....	.....	.....	109	53	56	.49	.....	....	0	1.2	0	..	..	7.57	....
1/7/53	...	..	...	...	....	1.3	..	.....	....	.....	.....	.....	....	....	....	.....	....	....	....	...	..	..	1.87	....
1/12/53	...	..	...	...	....	.....	..	.....	....	.....	.....	.....	....	....	....	.....	....	1+	7.4	3+	..	..	4.26	....
1/19/53	...	..	...	...	....	.....	..	.....	....	.....	.....	.....	....	....	....	6.5 3.7/2.8	....	4+	2.5	0	..	..	....	....
1/21/53	...	..	...	...	....	.....	..	.....	....	.....	.....	.....	....	....	....	.....	....	....	....	...	..	..	....	40

1/29/53	6.3	17	...	4.1	....	.....	..	.....	....	.....	.....	....	....	.....	....	....	...	..	.....	....
2/2/53	...	..	...	...	....	.....	..	.....	....	.....	.....	247	104	143	.42	.....	....	1+	2.8	2+	..	..	5.09	....
2/5/53	...	..	...	...	....	.....	..	.....	....	.....	.....	148	60	88	.41	8.0 4.6/3.4	....	3+	3.2	2+	..	..	.....	....
2/11/53	...	..	...	...	....	.....	..	10.2	....	.....	.....	.....	....	....	....	.....	....	....	....	...	..	..	.....	....
2/23/53	6.2	..	...	...	4.8†	7.2†	..	.....	630†	(7.5)	(11.5)	(164)	(56)	(108)	(.34)	6.64† 3.65/2.99	2+†	3+†	2.5†	0†	0†	9.0†	.....	....
3/12/53	6.1	..	...	5.2	....	6.2	0	0	....	.....	.....	.....	....	....	....	7.2 4.1/3.1	....	0	3.0	1+	..	..	5.3	....
3/25/53	...	..	...	...	....	.....	..	.....	484†	(6.9)	(9.5)	(222)	(73)	(149)	(.33)	6.96† 3.52/3.44	....	....	....	...	..	..	7.6†	....

* Abbreviations: Retic.—reticulocytes; W.B.C.—white blood cells; CCF—cephalin cholesterol flocculation; TT—thymol turbidity; TF—thymol flocculation; SCG—scarlet colloidal gold; SR—scarlet red; Shin.—Shinowara; Bod.—Bodansky.

** Determinations indicated by parentheses in texts "Related to Lipid Metabolism" were performed in the laboratory of Dr. I. J. Pincus, Jefferson Medical College. Those indicated by † were performed at the Graduate Hospital. All other determinations were made at the Philadelphia General Hospital.

moderate cardiac enlargement due to right and left ventricular hypertrophy. An electrocardiogram showed first degree heart block, and low T waves in leads 1, 2, 3 and CR4, 5 and 6, probably indicative of myocardial changes secondary to anemia. She received 1,000 ml. of blood prior to her discharge on April 16, 1949.

From April 16, 1949, to March 31, 1953, there were eight hospital admissions for the treatment of abdominal crises, two of which were severe. During each of these admissions she received 1,000 to 3,000 ml. of blood. During the four-year period between April, 1949, and her most recent admission, she received approximately 500 to 1,000 ml. of blood every month, and for a period she received transfusions every two weeks. In spite of this the hemoglobin and red blood cell counts were usually low, as may be seen in Table VI in which are recorded the results of some of the laboratory determinations during the four-year period of observation.

She was readmitted to the hospital for transfusion on March 31, 1953. Her mucous membranes appeared pale otherwise she looked well. Her weight was 120 pounds, height 5 feet 7 inches and she was approximately 17 per cent underweight. The blood pressure was 120/85 mm. Hg, temperature 99°F., pulse rate 85 per minute. The liver was considered to be enlarged but the edge, which was thought to be just above the level of the umbilicus in the right mid-clavicular line, could not be felt with certainty. Her heart was enlarged but to a lesser degree than on the first examination, and the murmurs were less intense.

On April 1, 1953, after eleven and one-half hours of fasting, a liver biopsy was performed at 8:20 A.M. Blood for tests was drawn from her antecubital vein between 8:15 and 8:25 A.M. The biopsy was performed without difficulty and a good specimen was obtained. A complication followed which has been reported elsewhere.[36] The results of the biochemical determinations at the time of biopsy are recorded in Table VI and of the electrophoretic analyses of serum proteins in Table II. Serum amylase and lipase values were 143 mg. per cent and 2.2 ml. N/20 NaOH, respectively. The blood sugar level was 101 mg. per cent.

Microscopic examination of the liver tissue obtained by needle biopsy revealed a striking picture. (Fig. 9.) There were massive amounts of pigment which gave a positive reaction for iron. It was present as fine granules or droplets

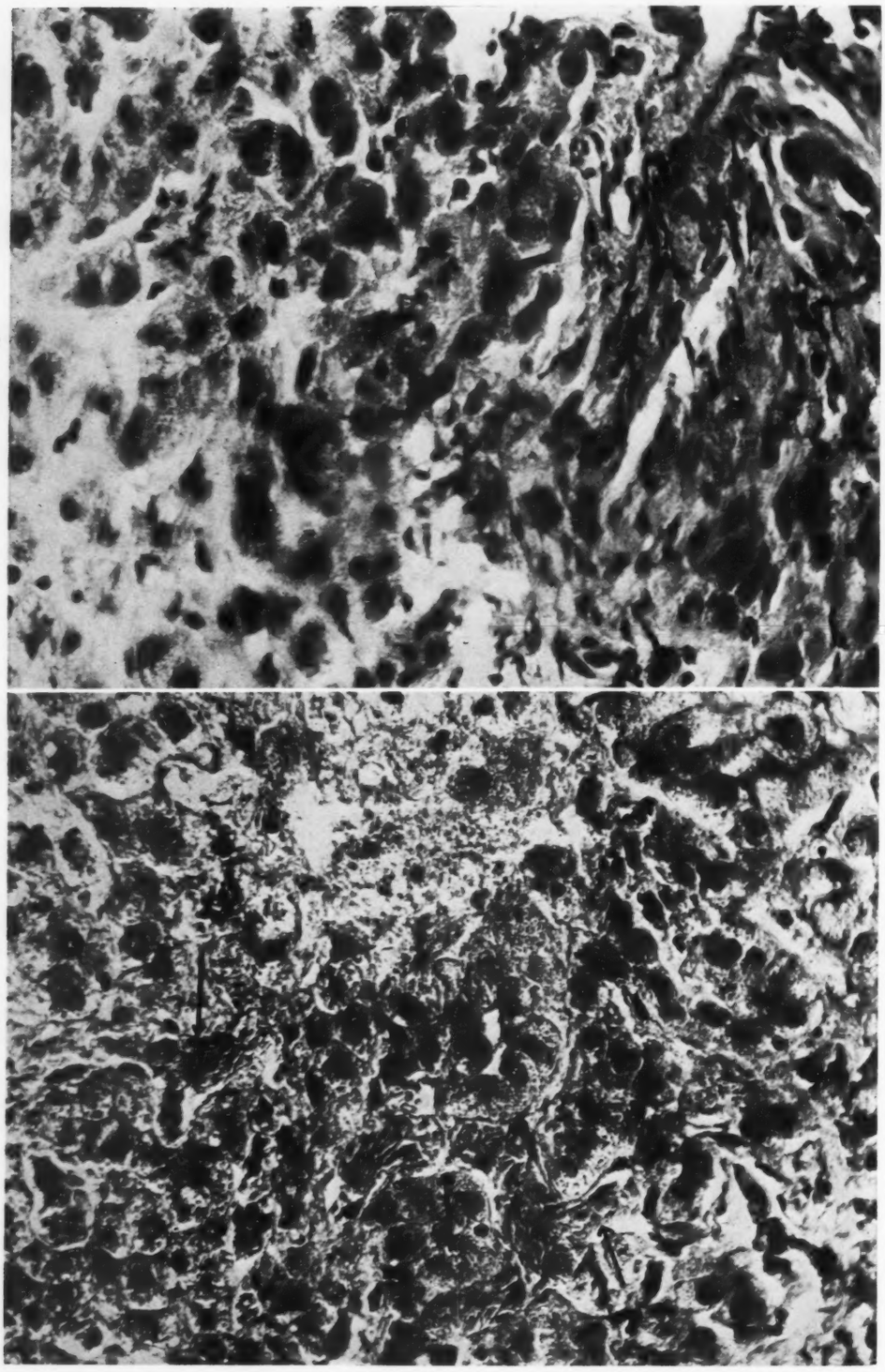


FIG. 7. Patient No. 3; high power view of fibrous tissue and adjacent degenerated parenchymal cells. In both the parenchymal cells and connective tissue are fine deposits of hemosiderin. Paraffin section (7 micra); hematoxylin and eosin; × 560.

FIG. 8. Patient No. 3. Adjacent to the area of parenchymal cell necrosis, there are many dilated sinusoids that are filled with clumped red blood cell masses (indicated by arrows). Paraffin section (7 micra); hematoxylin and eosin; B and G filters; × 350.

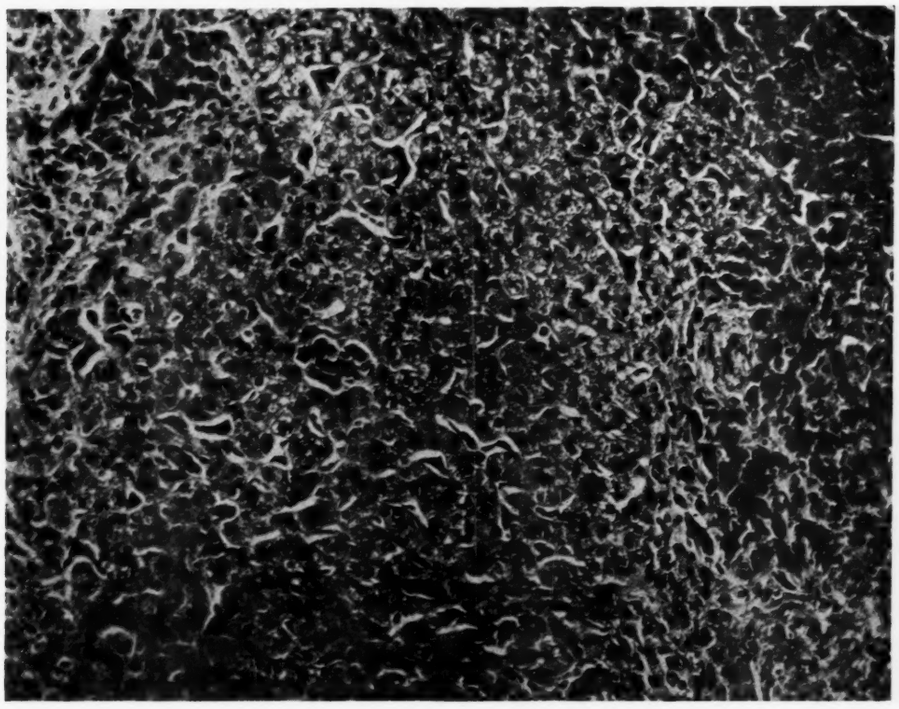


FIG. 9. Patient No. 4. Near the center of the photomicrograph is a focal area of degenerated parenchymal cells heavily laden with hemosiderin. In the upper left and lower right corners, fibrous replacement of the involved cells is prominent. Plugs of hemosiderin are seen in canaliculi, and Kupffer cells are filled with this pigment. Paraffin section (7 micra); hematoxylin and eosin; B and G filters; × 110.

in almost all of the parenchymal cells, in the Kupffer cells, and as plugs in the canaliculi. Focal areas of parenchymal cells containing iron were prominent. They showed no distinct zonal distribution. Frequently, bands of connective tissue, in which were deposits of iron, radiated from these sites to the portal areas. Deposits of hemosiderin were also prominent in the portal areas in which there was an increase in connective tissue. There were varying degrees of degeneration of parenchymal cells adjacent to connective tissue areas. Of interest were the deposits of iron in the arterial walls. There were only occasional small focal lesions in which parenchymal cells had "fallen out." Mallory stain revealed an increase in connective tissue of the portal areas and in areas in which iron-laden, degenerating parenchymal cells were replaced by fibrous tissue. The sinusoids were moderately dilated. No sinusoidal red cell clumps such as described in Case III were found.

As recorded in Table III, histochemical studies revealed no lipids in the biopsy specimen. The cytoplasm of the parenchymal cells contained a moderate amount of glycogen. About 1 per cent of the nuclei were vacuolated. There was probably no reduction in cytoplasmic pentose nucleic acids. Massive deposits of hemosiderin filled the parenchymal and Kupffer cells. No bile pigments could be seen.

COMMENTS

Liver Function Tests. Abnormal results for one or more of the "liver function tests," suggesting hepatic dysfunction, occurred in all of our patients. An increase in the serum concentration of direct-reacting bilirubin was almost always noted when hyperbilirubinemia was present and, in the absence of extrahepatic obstruction, was attributed to hepatic parenchymal involvement. A similarly high incidence of elevated direct reacting serum bilirubin levels has been reported by others. Thus of a total of fifty-one routine serum bilirubin determinations made by Henderson[2] in fifty-four patients with sickle cell anemia, twenty exhibited elevation of the direct-reacting bilirubin. Positive indirect reactions predominated during quiescent phases of the disease. Marked increases in direct-reacting bilirubin were associated with the largest and most painful livers although elevation of the indirect fraction also accompanied

TABLE VI

CASE IV—LABORATORY DATA*

Date	Hemoglobin	R.B.C.	Retic.	W.B.C.	Serum Bilirubin		Urine		Related to Lipid Metabolism							Related to Protein Metabolism							Serum Alk. Phosphatase	Bromsulfalein Retention %
					Direct†	Total	Bile	Urobilinogen‡	Total Serum Lipids	Serum Phospholipids	Serum Fatty Acids	Serum Cholesterol				Total Serum Proteins Albumin/Globulin	CCF		TT	TF	SCG	SR		
												Total	Free	Ester	Free/Total Ratio		(24 hr.)	(48 hr.)						
Normal	13.0–15.0 gm./100 cc.	4.2–5.4 million/cu. mm.	Up to 1.5%	5–10 thousand/cu. mm.	Up to .4 mg. %	Up to 1.0 mg. %	0	.1 to 1.2 E. units/2 hr. (Up to 1/20)	500–800 mg. %	9–10 mg. % P	7.2–16.2 mEq./L.	150–230 mg. %	50–30% of total	50–70% of total	Up to .5	6.0–8.0 gm. % 4.5–5.0/1.5–3.0 gm. %	0–1+	0–2+	1.0–4.0	0–2+	0–2+	0–2+	1.5–5.0 Bodansky units	Dose—5 mg./kg. body wt. Normal less than 5% in 45 min.
4/12/49	6.0	2.0	15.1	....	.....	....	..	.....	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
4/13/49	10.0	3.6	13.9	8.5	.....	1.4	..	.....	...	..	..	220	100	120	.45	6.48 3.92/2.56	...	...	...	...	...	...	...	....
4/15/49	....	...	....	....	.....	....	..	.....	...	..	..	...	...	...	...	.....	0	1+	2.0	±	2+	2+	...	....
4/27/49	7.5	2.9	.4	2.2	Neg.	.3	..	.....	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
8/14/49	9.5	3.7	....	....	Immed.	2.0	..	.....	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
8/15/49	11.5	4.1	12.0	9.3	.....	....	..	.....	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
8/16/49	13.0	3.2	....	4.2	.....	....	..	.....	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
8/18/49	13.0	4.4	....	5.9	.....	....	..	.....	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
9/15/49	8.5	3.1	....	....	.....	....	..	.....	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
10/4/49	7.0	2.6	....	....	.....	....	..	.....	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
10/6/49	10.5	3.7	....	....	Neg.	.6	..	.....	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
1/11/50	6.0	2.1	....	....	.....	....	..	.....	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
1/12/50	9.5	2.8	....	....	Immed.	3.0	..	(0)	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
1/13/50	8.5	2.5	9.9	....	Immed.	4.0	..	(0)	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
1/14/50	8.0	2.3	5.3	....	Immed.	2.0	..	.....	...	..	..	...	...	...	...	.....	0	0	1.0	0	0	0	...	....
1/16/50	11.0	3.1	1.7	40.0	Immed.	3.0	..	(1/20)	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....

TABLE VI (*Continued*)

Date	Hemoglobin	R.B.C.	Retic.	W.B.C.	Serum Bilirubin		Urine		Related to Lipid Metabolism							Related to Protein Metabolism							Serum Alk. Phosphatase	Bromsulfalein Retention %
					Direct†	Total	Bile	Urobilinogen‡	Total Serum Lipids	Serum Phospholipids	Serum Fatty Acids	Serum Cholesterol				Total Serum Proteins Albumin/Globulin	CCF		TT	TF	SCG	SR		
												Total	Free	Ester	Free/Total Ratio		(24 hr.)	(48 hr.)						
Normal	13.0–15.0 gm./100 cc.	4.2–5.4 million/cu. mm.	Up to 1.5%	5–10 thousand/cu. mm.	Up to .4 mg. %	Up to 1.0 mg. %	0	.1 to 1.2 E. units/2 hr. (Up to 1/20)	500–800 mg. %	9–10 mg. % P	7.2–16.2 mEq./L.	150–230 mg. %	50–30% of total	50–70% of total	Up to .5	6.0–8.0 gm. % 4.5–5.0/1.5–3.0 gm. %	0–1+	0–2+	1.0–4.0	0–2+	0–2+	0–2+	1.5–5.0 Bodansky units	Dose—5 mg./kg. body wt. Normal less than 5% in 45 min.
1/17/50	10.0	2.8	1.3	10.0	Del.	1.5	..	.....	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
1/23/50	9.5	2.8	....	....	Neg.	.2	..	.....	...	..	..	...	...	...	...	6.68 3.98/2.70	0	0	1.5	0	0	0	...	....
10/3/50	5.0	2.1	....	....	.....	....	..	.....	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
4/12/51	6.3	2.5	3.1	12.3	.3	1.3	..	.....	...	..	..	180	64	116	.36	6.32 3.65/2.67	0	0	2.0	0	0	0	.8	....
4/13/51	....	...	....	....	.....	....	0	(1/20)	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	36.0
4/16/51	11.0	3.8	1.3	....	.35	.88	0	(0)	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
8/10/51	5.0	1.8	....	6.0	.....	....	..	.....	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
4/18/52	5.5	2.0	....	....	.....	....	..	.....	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
10/4/52	9.3	3.3	....	....	.27	.75	..	.....	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
10/10/52	....	...	....	....	0	.3	..	.2	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
12/19/52	10.3	3.6	....	....	Del.	.8	..	.....	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
3/31/52	7.0	2.8	....	....	.....	....	0	(0)	...	..	..	...	...	...	...	.....	...	...	...	...	...	...	...	....
4/1/53	8.0	2.4	....	5.7	.37	.81	..	.....	434	..	..	168	138	30	.82	7.52 4.18/3.34	2+	2+	3.5	2+	±	±	2.4	....

* Abbreviations: R.B.C.—red blood cells; Retic.—reticulocytes; W.B.C.—white blood cells; CCF—cephalin cholesterol flocculation; TT—thymol turbidity; TF—thymol flocculation; SCG—scarlet colloidal gold; SR—scarlet red.

† In some instances the direct reacting serum bilirubin was determined qualitatively: del.—delayed; immed.—immediate; neg.—negative.

‡ For values in parentheses all tests positive in dilutions less than 1/20 are recorded as 0.

hepatomegaly. Henderson suggested that when cholelithiasis is excluded the presence of direct-reacting bilirubin suggests associated "cholangiolar dysfunction." Green[8] and his coworkers observed that in some patients very marked elevation of serum bilirubin occurred on occasion, usually during crises. Their cases also showed a significantly high proportion of increased direct-reacting bilirubin levels, bilirubinuria and marked evidence of hepatic dysfunction.

Although Wintrobe[37] has stated that "remissions in this disease are never of such degree that no icterus was present," our patient in Case IV had normal direct-reacting and total serum bilirubin values on several occasions throughout the four-year period of observation in this hospital. Increased urinary urobilinogen excretion due to hemolysis, hepatic disease or both occurred at varying periods during the illness of all but the patient in Case IV. Bilirubinuria was demonstrated in Cases I and II. It is likely that had urinalyses been performed at appropriate times the remaining patients also would have exhibited bilirubin and excess urobilinogen excretion. In those with marked "cholangiolar damage" studied by Henderson[2] there was a fall in the fecal urobilinogen excretion, whereas, without evidence of liver damage, the fecal urobilinogen was high.

The almost constant finding of hypoalbuminemia in Cases I, II and IV, and the frequently decreased levels in Case III is significant and probably indicative, for the most part, of hepatic dysfunction. Serum globulin values varied. They were usually elevated in Case I but usually normal in the others. However, hyperglobulinemia was present in the fourth patient at the time of her liver biopsy and in the patient in Case III when his second biopsy was taken. In this small group of patients there appeared to be no relation between the occurrence of sickle cell crises and the presence of hyperglobulinemia. Because the method used for fractionating serum proteins may not give adequate separation of albumin and globulins, the results of the serum proteins studied by the Tiselius method performed in three of the patients are of interest. As noted in Table II, there was a decrease in the proportion of albumin and an increase in globulins. Among the globulins, the gamma fraction was the one most consistently elevated although some increase in the alpha$_2$ fraction was noted in one patient (Case I) and in the beta fraction in another (Case II), while there was a tendency for the alpha$_1$ globulin to be decreased in all three. These observations generally agree with those reported by Murphy and Shapiro[38] for one case and by Fenichel, Watson and Eirich[6] for fifteen cases of sickle cell anemia studied electrophoretically. These abnormalities of serum proteins are relatively common in various diseases, especially those with some accompanying impairment of liver function such as acute hepatitis or cirrhosis.[39–44] Similarly, the occurrence of a fraction with a mobility between the alpha$_2$ and beta globulins has been noted in other diseases. It is associated with serum lipids and may represent lipoprotein.[45] Fenichel, Watson and Eirich[6] believed that the changes in the serum proteins found in their cases were secondary to the general disease process, especially in the liver, caused by the sickle cell anemia.

Following the initial abnormal cephalin-cholesterol flocculation test (forty-eight hours) in Case I, all subsequent determinations were normal. The results of this test were normal in the second and fourth patients and varied throughout the course of the illness in Case III. The initial thymol flocculation test was abnormal in Case I and the thymol turbidity was subsequently only minimally elevated on one occasion. All other determinations of these and the serum colloidal gold and scarlet red tests were normal. There was no correlation between serum protein disturbances and abnormalities in these "turbidity and flocculation" tests performed on the same bloods taken at the times of biopsy. The importance of serial determinations in assessing liver function tests is apparent from a study of the findings in our first patient. It is difficult to appraise reports dealing with abnormalities of these tests unless there is some indication of the number performed and their relation to the illness.

Serum alkaline phosphatase levels fluctuated but were usually elevated in three of the four patients. There was no constant relation between the levels of this enzyme and the histologic hepatic abnormalities or other biochemical findings. Before ascribing elevations in serum alkaline phosphatase to liver disease, the possibility that bone lesions are present must be considered. Radiologic evidence of bony involvement was present in only one patient (Case II). Because osseous changes in patients with sickle cell anemia may not be radiologically

evident, it is still possible that these were present in the other two patients studied. Unless the possibility of bony involvement is considered, the use of serum alkaline phosphatase determinations in conjunction with turbidity and flocculation tests to establish a differential diagnosis between hepatic and posthepatic jaundice may result in incorrect interpretations. When elevations of serum alkaline phosphatase levels are due to liver disease, it is of interest to postulate that one mechanism for the raised values may be canalicular narrowing and obstruction consequent to sinusoidal widening which is so common a finding in this disease.

As may be noted in Tables I, IV, V and VI, some abnormality of serum lipids existed in all four patients. In view of the small number of patients and the complex problems associated with the interpretation of serum lipid levels in relation to primary liver dysfunction, no conclusions can be drawn.

Bromsulfalein retention was borderline in Case I but considerably increased in the other three patients. However, the elevation in the patient in Case II must be considered in relation to the hyperbilirubinemia extant when the bromsulfalein retention was determined. The frequent elevation of serum amylase and lipase levels in our patients is of interest, as occurring in a disease whose abdominal manifestations may be confused with acute primary pancreatitis.

Histologic Findings. The occurrence of "interstitial fibrosis"[46] and of cirrhosis has been described in patients with sickle cell anemia. Green, Conley and Berthrong[8] found advanced, nodular cirrhosis in four of twenty-one patients with sickle cell anemia at autopsy. Two of these were considered to be of the postnecrotic variety and two were not classified. There were trivial pigment deposits in two of the cirrhotic livers but one contained large amounts of iron-positive pigment in the parenchymal and Kupffer cells without pigmentation of the scar. Three of our patients had cirrhosis. Of these, one (Case IV) had hemochromatosis which was probably related to multiple blood transfusions. A case of exogenous hemochromatosis in a child with sickle cell anemia has been described by Frumin and Miller.[47] In the first liver biopsy specimen of the patient in Case II in whom portal cirrhosis developed over a period of three years, there were moderate amounts of iron-containing pigment in the parenchymal and Kupffer cells but none in the fibrous tissue scars. Although there was insufficient tissue to make a diagnosis of the type of cirrhosis with certainty in Case III, it was considered to be portal in type. The parenchymal cells were well filled with hemosiderin and small amounts of iron-containing pigment were also present in the connective tissue scars. Although, unlike the patient in Case IV, no striking relation between degeneration and necrosis of iron-laden parenchymal cells and fibrosis was evident, the possibility that the cirrhosis was related to hemosiderosis, the result of breakdown of exogenous and/or endogenous red blood cells, cannot be excluded with certainty. If in Case III hemosiderosis was not the initiating cause, it might have acted as an accelerating factor in the development of the cirrhosis. The possibility that hepatocellular damage may occur should be considered when multiple transfusions are used in an attempt to maintain higher levels of hemoglobin in this disease.

In Case II there was no history of alcoholism, deficient diet or other known factors that might have played a role in the development of cirrhosis. The dietary intake of the patient in Case III was considered inadequate and may possibly have played some role. As has been noted by Green et al.,[8] chronic anemia would not appear to be an important factor in the pathogenesis of cirrhosis. Nor did chronic congestive failure appear to be related to the cirrhosis in our cases. The absence of intratrabecular fatty cysts in Cases II and III makes it unlikely that a fatty liver antedated the cirrhosis.[48] It is not possible to exclude an element of viral hepatitis with consequent cirrhosis in our three patients. It is possible, however, that the portal cirrhosis in these patients may be unrelated to any known pathogenetic factor. Certainly this is true of many patients without sickle cell anemia.

Varying degrees of hepatic parenchymal degeneration and/or necrosis were found in our cases irrespective of other pathologic conditions present. Green et al.[8] have reported the occurrence of tiny focal or large lesions where liver cells had been lost, focal necrosis of the liver parenchyma, centrilobular necrosis, as well as diffuse atrophy most noticeable in central zones. Small focal hepatic necroses have also been noted by Diggs and Jones.[49] Scattered large foci of necrosis of the liver have been described in a patient with sickle cell anemia by Kimmelstiel.[50] No vascular occlusion was found and he concluded that the lesions were the result of acute

vascular spasm. The occurrence of severe widespread necrosis has also been reported by Green et al.[8] Our findings in liver biopsy material permit a more accurate interpretation because of the elimination of possible alterations due to terminal states or postmortem changes.

Focal hepatic parenchymal lesions were present in all of our cases. These varied in type, size and number. None showed a distinct zonal relation. Some were small and appeared as if a few liver cells "had fallen out." In some the parenchymal cells were degenerated and the nuclei were pyknotic. In some focal areas necrosis was evident. (Fig. 3.) Reticular stains usually revealed collapse of the supporting reticulin. Similar small focal parenchymal lesions have been also described in patients with portal cirrhosis, diabetes mellitus and in other liver diseases.[7]

In patients with sickle cell anemia, several possible causes for these focal lesions deserve consideration. It is considered too that the various focal lesions may have independent causes and may vary in significance. The role of iron-containing pigment as a cause of focal parenchymal degeneration has already been noted.

Engorgement of dilated hepatic sinusoids by red cell clumps was present in patients in Cases II, III and IV and in the second biopsy of the first patient. The most striking example of focal hepatic necrosis apparently related to ischemia occurred in our Case III. As demonstrated in Figure 8, the sinusoids surrounding much of this focal necrotic lesion were obstructed by masses of clumped red cells. It is conceivable that lesser degrees of parenchymal cell degeneration or necrosis might also result from sinusoidal blockades by masses of clumped red cells. It is probable that this cause of focal parenchymal necrosis occurs only in sickle cell anemia.

That Kupffer cells, engorged by phagocytosed erythrocytes, might also result in sinusoidal obstruction has been suggested by Green, Conley and Berthrong.[8] Kupffer cell prominence of varying degree was a constant finding in our patients and was most marked in Cases III and IV. Usually the cytoplasm of the Kupffer cells was filled with débris, some of which stained as hemosiderin. Their nuclei sometimes bordered the clumps of red cells, which appeared to have been phagocytosed. However, clumps of red cells in sinusoids were usually unassociated with Kupffer cells, and extreme prominence of these phagocytes sufficient to cause sinusoidal obstruction or sinusoidal widening as described by Green et al.[8] did not appear to be a feature of our cases.

It is conceivable that the marked and unexplained narrowing of small arteries in our patient in Case II might predispose to thrombosis especially in the presence of sickle cell disease. It is of interest to postulate that in this patient the cardiac enlargement unassociated with hypertension, the pulmonary lesions and the hepatic cirrhosis might all be related to vascular changes similar to those found in the liver. However, the excellent collateral circulation within the liver would make it seem unlikely that partial arrest of the circulation in only some of the vessels of this size would account for the parenchymal changes noted. As has been indicated, a more plausible explanation for some of the parenchymal changes found is the occurrence of vascular obstruction more distally, in the hepatic sinusoids, by masses of sickled red cells.

It is conceivable that if the focal lesions are large and particularly when necrosis is striking, as illustrated in Figure 8, collapse of the supporting reticulum followed by fibrosis may supervene. It is considered likely that the absence of any distinct zonal distribution and the recurrence of these lesions might favor the development of a multilobular cirrhosis. However, in the limited tissue provided by needle biopsy no definite relationship could be shown between any of the focal lesions and the development of cirrhosis in these patients.

In addition to the possible vascular causes of the parenchymal lesions, it is interesting to postulate that during crises and/or periods of hemolysis, a "toxic agent," possibly liberated as the result of an antigen-antibody reaction, may act as a hepatotoxin and be responsible for some of the parenchymal changes described, such as occurred in our first patient.

Histochemical Observations. The histochemical findings in the liver biopsies of all four patients are essentially the same. (Table III.) In the cytoplasm of the parenchymal cells one noted mere traces of demonstrable lipids or none at all, moderate to large amounts of uniformly distributed glycogen and large amounts of pentose nucleic acids. In their nuclei, there may have been some decrease in the content of desoxypentose nucleic acids.

The results of the histochemical tests revealed

no significant or characteristic change in the liver in sickle cell anemia. Correlations could not be established between the histochemical observations and the various biochemical findings for this small group of patients.

In most textbooks of pathology severe anemia has long been stated to be a cause of fatty degeneration in various organs, including the liver. Moreover, the tendency to stasis and the obstruction of sinusoids by sickled cells is a further complication in this form of anemia. Even so, hepatic fatty metamorphosis was negligible in our cases as well as in those reported by Green, Conley and Berthrong.[8] This may be related to the chronicity of the disease and its onset in early life. The negligible amounts of histochemically demonstrable liver lipids is also of interest since the patients had been fasting for about twelve hours when the biopsies were taken. In view of previous observations,[7] this may be considered unusual and possibly reflect another effect of sickle cell anemia on hepatocellular function.

The individual differences in cytoplasmic glycogen are not remarkable and are such as might be anticipated for any group of subjects studied under the same conditions. The occurrence of glycogen within the parenchymal cell nuclei in two of the patients is abnormal but may be encountered in a variety of liver disorders.[7,51] Its cause remains unknown. Considering that the tissues were fixed in ethanol, usually for several days, the observations on nucleic acids are probably unreliable[51,53] even though consistent. The apparently large amounts of pentose nucleic acids in the cytoplasm, however, suggest ample cytoplasmic protein despite disturbances in plasma proteins suggestive of hepatocellular dysfunction.

SUMMARY

Clinical and biochemical studies and histologic and histochemical observations on liver tissue obtained by needle biopsy were made on four patients with sickle cell anemia. There was one instance of hepatitis, one of hemochromatosis and two of portal cirrhosis. Serial liver function tests were performed in each case. The significance of the tests in this disease is discussed and the importance of serial determinations is indicated. Because osseous involvement in the absence of radiologic evidence may occur in sickle cell anemia, the serum alkaline phosphatase test is of limited value as an aid in differentiating jaundice of hepatic from posthepatic origin. Hypoalbuminemia and hyperglobulinemia, with elevation of the gamma fraction and a decrease in the alpha$_1$ globulin values, were the most consistent serum protein alterations.

The finding of elevated serum amylase and lipase values in this disease is of interest in view of its abdominal manifestations which may be confused with acute primary pancreatitis.

Hepatitis in one patient was thought to be a manifestation of the sickle cell disease *per se*. Focal parenchymal lesions were found in the liver of this patient during the recovery stage and in the liver specimens of the other three patients. They varied in type and in size. The possible causes of these changes are discussed. Ischemia, the result of sinusoidal obstruction by red cell clumps, would appear to be the most likely cause of some of them. That some of the parenchymal changes may be due to a "hepatotoxin" associated with sickle cell crises deserves consideration.

The likelihood that some of the necrotic lesions, when prominent and repeated, may be followed by cirrhosis as another hepatic manifestation of sickle cell anemia is noted. The precise role of iron-containing pigment in the pathogenesis of the cirrhosis in one of our patients is in doubt. Hemochromatosis in one patient was unquestionably related to multiple blood transfusions. The possibility of hepatic damage consequent to multiple blood transfusions given to maintain hemoglobin levels in this disease deserves consideration.

Histochemical studies revealed no or only mere traces of demonstrable lipids in the cytoplasm of the parenchymal cells. This is of interest in view of the anemia extant in these patients who were fasting at the time of biopsy. No characteristic changes in glycogen or nucleic acids were found.

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Seminars on Carbohydrate Metabolism

Recent Developments in the Field of Glycogen Metabolism and the Diseases of Glycogen Storage*

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IN 1929 von Gierke described a disease characterized by enlargement of the liver and kidneys with extensive deposition of glycogen in these organs.[1] Following the original description of glycogen storage disease, some fifty additional cases reached the literature by 1946,[2] and many more have been diagnosed and reported since.[3] Although the disease is relatively rare, the nature of the derangement in carbohydrate metabolism has assumed considerable interest for both the biochemist and clinician.

Schoenheimer[4] showed that the glycogen isolated from von Gierke's original case could be degraded by minced normal human liver, demonstrating the likelihood that the diseased liver is deficient in a fundamental mechanism required for glycogen degradation. However, systematic approach to the study of the disorder was not possible until relatively recent years since the accumulation of biochemical knowledge concerning the enzymatic processes involved in the synthesis and degradation of glycogen in the body was necessary. Particularly outstanding contributions to this field have been made by Carl and Gerty Cori but other workers have shared in the development of this fundamental knowledge.[5]

Central to the entire system of carbohydrate metabolism are the processes of glycogenesis and glycogenolysis, that is, the formation and breakdown of glycogen. These reactions, in as much as they influence the availability of glycogen, affect the overall metabolism of the organism in a profound way such as (1) maintaining the blood sugar level for cerebral and other vital organ functions, (2) making available sources of energy for other synthetic processes (protein and fat) and (3) providing a store of reserve energy which may be made available in times of stress (starvation). Therefore, disorders of metabolism which limit the availability of glycogen exert far-reaching effects demonstrable chiefly as hypoglycemia and impaired protein synthesis and growth.

It is the purpose of this paper to consider the metabolism of glycogen in the normal individual in the light of newly developed biochemical concepts. With this as background, attention will be directed to the diseases of glycogen storage, and an attempt will be made to correlate the clinical, biochemical and pathologic observations with a view toward a more complete understanding of the nature of the defects in these disorders.

GLYCOGEN METABOLISM IN THE NORMAL SUBJECT

Molecular Structure and Distribution of Glycogen. Glycogen or animal starch is a branched polysaccharide composed entirely of glucose units.[6] These units are arranged in chains with linkage between the first and fourth carbon atoms of adjacent units. Branch points of the molecule are established with linkage between the first and sixth carbon atoms. The molecule has been compared to a tree with a single free glucose unit (reducing end) and successive tiers of non-reducing units in the 1–4 linkage. The tiers are the result of successive and increasing numbers of branch points. (Fig. 1.) This

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concept of structure has been presented by G. T. Cori[7] and its formulation is the result of a series of ingenious studies concerning the enzymatic mechanisms of synthesis and stepwise degradation of glycogen. Molecular weight of the branched molecule is polydisperse and is of the order of one to four million or greater.[8]

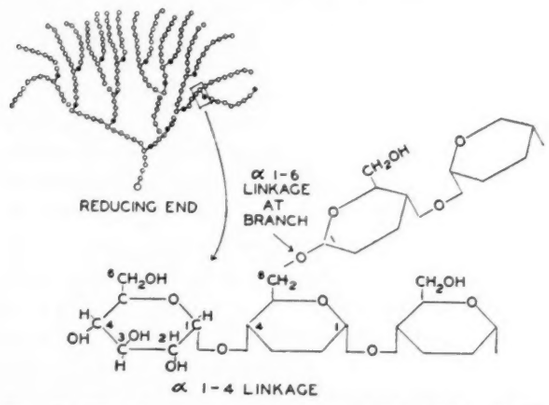
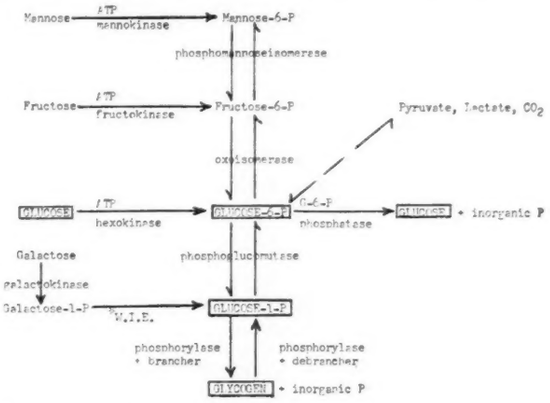


FIG. 1. The glycogen molecule as depicted by G. T. Cori.[18] Open circles are alpha 1–4 glucosidic links and solid circles are 1–6 links. Segment at the branch point is enlarged to show structure.

Glycogen formation occurs in practically every tissue of the body. Liver and muscle, however, are major sites of metabolism. Although small quantities may be found in most tissues, it is only in the liver and muscle that significant quantities are found. It is difficult if not impossible to state the normal range of concentration for liver and muscle glycogen since autopsy and biopsy specimens are subject to rapid glycogen breakdown. The nutritional status of the organism influences the level markedly and the degree of sympathetic nervous activity (epinephrine) alters the level. The capacity of the liver to store glycogen is not unlimited, and in rabbits fed high carbohydrate diets a glycogen level greater than 18 to 20 per cent is not exceeded, although under these conditions fat accumulates.[9] It is noteworthy, however, that in her studies of human glycogen Cori found concentrations ranging from 0.56 to 4.6 per cent in normal infant liver and 0.56 to 0.96 per cent in muscle specimens.[10]

Synthesis and Degradation of Glycogen. Ingestion of a variety of carbohydrates including glucose, fructose, galactose, and mannose lead to the deposition of glycogen in the liver. (Fig. 2.) Glucose is phosphorylated at the expense of ATP by the enzyme hexokinase, and the product glucose-6-phosphate is transformed by phosphoglucomutase to glucose-1-phosphate, which is the primary substrate from which glycogen is formed. Fructose is similarly phosphorylated by fructokinase and the fructose-6-phosphate derivative is converted by oxoisomerase to glucose-6-phosphate and hence to glucose-1-phosphate which gives rise to glycogen. Mannose is also



*Walden Inversion Enzyme.

FIG. 2. Enzymatic reactions involved in glycogen synthesis and degradation in liver.

phosphorylated to the 6-phosphate and in the presence of a phosphomannose-isomerase and oxoisomerase is converted to an equilibrium mixture of the 6-phosphate esters of fructose and glucose. Galactose is phosphorylated to galactose-1-phosphate by its specific kinase, after which a second enzyme system, Walden inversion enzyme, in the presence of a coenzyme uridine-di-phosphoglucose converts the product to glucose-1-phosphate.[11] Other metabolites are capable of forming glycogen if conversion to glucose-1-phosphate can be achieved. In this category are lactic acid, amino acids, propionic acid and glycerol. Following formation of glucose-1-phosphate, synthesis of the glycogen molecule succeeds by a progression of enzymatic reactions. Phosphorylase acts to remove the phosphate group from glucose-1-phosphate and attaches the bared first carbon atom to the fourth carbon of a glucose residue on the glycogen nidus.[12] This addition occurs on the non-reducing end of the molecule. In this way successively longer 1–4 glucose chains are added. This reaction is reversible and the direction, that is, glycogen synthesis as opposed to breakdown, is dependent on the ratio of inorganic phosphate to glucose-1-phosphate. At pH 7.0 synthesis occurs if more than one mole of glucose-1-phosphate per three moles of inorganic phosphate are in contact with the

enzyme. Thus a high level of inorganic phosphate favors glycogen breakdown. When the chain has been lengthened to a critical level of eight glucose residues, the molecule becomes the substrate for the second enzyme known as the branching enzyme, which transfers the alpha 1–4 linkage to an alpha 1–6 linkage, establishing a branch point of the molecule. Larner[13] very clearly demonstrated that this enzyme is indeed a transglucosidase by showing that on incubation with brancher glycogen containing C^{14} labeled 1–4 linkages developed 1–6 linkages which were labeled with C^{14}. In this way the glycogen molecule is synthesized.

Still another enzyme is required for degradation of glycogen since brancher activity is not reversible. This enzyme is called debrancher, has been isolated from muscle and liver[14] and causes hydrolytic cleavage of the 1–6 linkage, liberating glucose. It can only act, however, after phosphorylase, in the presence of inorganic phosphate, has systematically removed the 1–4 linked glucose residues from the outermost tier, converted these to glucose-1-phosphate and bared the branch points or the 1–6 links. Cori[15] has shown that phosphorylase degrades glycogen to a product called limit dextrin or LD wherein the outermost tier of glucose residues is removed to the branch points. Then debrancher acts and the penultimate tier becomes the outermost tier. Thus, by a series of orderly reactions the glycogen molecule is degraded. Because of the reversibility of the mutase enzyme the product, glucose-1-phosphate, is converted to glucose-6-phosphate. In liver and kidney this ester is split by a specific glucose-6-phosphatase to free glucose and inorganic phosphate, while in muscle, which lacks this phosphatase, the 6-ester is converted almost entirely to lactic acid or is oxidized. Free glucose liberated in the liver enters the blood stream, and in this way the importance of this phosphatase reaction for maintenance of a normal concentration of blood sugar may be seen.

Glycogen in the Fetus. Since certain of the disorders of glycogen metabolism are known to be familial and present at birth, it is of interest to consider the information available concerning the various glycogenic enzymes in the fetus. Studies of glycogen formation in the liver of the fetal guinea pig have demonstrated that three distinct phases are involved: (1) No glycogen is demonstrable in the liver before the fifty-seventh day of the sixty-six day gestation period. (2) Glycogen accumulates rapidly in the liver from the fifty-seventh day until term, when the concentration is two to three times that of the liver of the mother. (3) Liver glycogen is rapidly depleted following birth. In phase 1, all enzymes other than brancher enzymes concerned with glycogen synthesis are known to be present. It is thought that an increase in brancher initiates phase 2.[16] Nemeth has shown that glucose-6-phosphatase is absent until term.[17] Thus glycogen may accumulate in phase 2 since glucose-6-phosphate cannot be readily degraded and phosphohexokinase activity is relatively slow. Finally, concomitant with the appearance of glucose-6-phosphatase at birth glycogen is rapidly depleted. It is certainly of more than academic interest that a condition of glycogen storage, associated with a deficiency of the specific glucose-6-phosphatase, exists in the normal fetus.

Determination of Glycogen Structure. When the ability to synthesize glycogen is established in a tissue, molecular structure is dependent upon the ratio of activities of three enzymes, namely, phosphorylase, brancher, and debrancher.[18] Since the methods of analysis used by Illingworth and Cori[10] to determine the structure of normal glycogen have been utilized in the analysis of storage disease glycogen, these two methods are briefly outlined.

End-group analysis (enzymatic branch-point analysis): The glycogen sample is incubated with inorganic phosphate, phosphorylase and debrancher. Free glucose appears as a result of the debrancher action on each 1–6 link while glucose-1-phosphate appears as a result of the phosphorylase action on the 1–4 links in the outer chains. Thus, the ratio of 1–6/1–4 links is equivalent to the per cent of branch points and may be used in describing the configuration of the glycogen molecule.

Successive and alternating degradation using phosphorylase and debrancher: The first limit dextrin is isolated and by estimation of glucose-1-phosphate the outer chain length is determined. Debrancher action then determines the per cent of branch points. "After the first tier of branch points has been removed by action of glucosidase on LD_1, the debrancher enzyme is inactivated by heat and phosphorylase is added. This results in the formation of LD_2 which is again isolated, and so on. Each successive LD differs from the preceding one by the removal of one tier. Up to four successive LD's were isolated

from liver glycogen, by which time the degradation had reached 90 per cent. The analytical data obtained after each enzymatic step could be made to fit only one kind of model, namely, that which represents the polysaccharide as multibranched tree-like structures. If this structure were completely regular, there would be 50 per cent of all the branch points in the first tier, 25 per cent in the second, 12.5 per cent in the third, and so on. The percentages found in normal human liver glycogen were, however, 40, 25, and 10 per cent, respectively."[7] This implies a somewhat irregular structure.

Using these methods Illingworth, Larner and Cori[15] characterized the structure of normal rabbit glycogen in various states of nutrition, the structure of cat and fetal sheep glycogen and that of five samples of normal human glycogen.[10] Results are reproduced in Table 1 and indicate that human glycogen is very similar to animal glycogen in structure. Further, it is apparent that newly-formed glycogens after a period of fasting have longer outer chains and are less branched, while the reverse is true of older glycogens.

Factors Regulating the Concentration of Glycogen in the Tissues. One of the major defects in glycogen storage disease concerns the increased concentration of glycogen in the tissues. In considering the nature of the defect it seems worthwhile to comment on the variety of factors in the individual which influence tissue levels of glycogen. These factors are numerous and include hormones, electrolytes and enzymes; in addition, the nutritional state and certain diseases may affect these levels.

A well known phenomenon is the depletion of liver glycogen in fasted animals and the reverse situation in animals which are fed high carbohydrate diets. Stetten has shown in the rabbit that about 3 per cent of the ingested carbohydrate is converted to glycogen,[19] so that with an extremely high intake it is conceivable that liver glycogen may rise considerably. Further, any substance which increases the glucose uptake of tissues increases glycogen levels, and materials which inhibit glucose uptake have the opposite effect.

The role of insulin and the diabetogenic hormones must be mentioned in this regard. Insulin increases glucose uptake of isolated muscle[20] as well as glycogen synthesis in these tissues. An insulin effect upon hepatic glucose uptake has also been demonstrated but this is apparent *in vivo* only.[21] The exact mechanism by which this insulin action is accomplished is not clear, although an effect upon the hexokinase system is a favored hypothesis.[22,23] In experimental animals in the absence of insulin or in uncontrolled diabetes the liver glycogen is low.

TABLE 1
ANALYSIS OF GLYCOGEN STRUCTURE

Source of Glycogen	1–6 Links (%)	Degradation by Phosphorylase (%)
*Liver glycogen:		
Rabbit	6.8	36.2
Cat	8.1	28.0
Fetal sheep	8.7	36.6
†Human liver:		
Infant	7.1	31.9
Infant	8.4	41.0
Human muscle:		
Leg	8.0	34.6
Pectoralis	7.2	32.7
Pectoralis	8.1	25.0

* Data obtained from C. F. Cori.[7]
† Data obtained from B. Illingworth and G. T. Cori.[10]

Bondy[24] has also demonstrated that the human diabetic has decreased liver glycogen levels. A recent observation in the alloxan diabetic animal is of special interest. Langdon has shown that in diabetic rats the activity of the glucose-6-phosphatase of liver is markedly increased, and has suggested that this is in part responsible for an increased liberation of glucose from the liver in diabetes.[25] Administration of insulin results in fall in the activity of this enzyme to normal. In view of the fact that hyperinsulinism might conceivably lead to diminished glucose-6-phosphatase activity and increased glycogen storage, the author reviewed the autopsy findings in several patients who died of functional pancreatic adenomas. No evidence of increased glycogen in tissues could be found.[26]

With respect to inhibitors of glucose uptake, it is known that pituitary growth hormone and adrenal steroids decrease glucose uptake of muscle[27] and secondarily decrease glycogen synthesis. Adrouny and Russell[28] found that hypophysectomized rats rapidly deplete stores of liver glycogen and, on administration of

growth hormone, loss of glycogen from the liver is diminished. Further, in the normal fasted animal, with depletion of liver and muscle glycogen the levels of cardiac glycogen increase. This increase does not occur in hypophysectomized fasted rats unless a growth hormone is administered. It is concluded, therefore, that the growth hormone is glycostatic with respect to the liver but actually increases the glycogen content of heart muscle.

TABLE II
FACTORS AFFECTING CONCENTRATION OF GLYCOGEN IN TISSUES

Increasing	Decreasing
High CHO intake	Starvation
Insulin	Insulin deficiency
Adrenal steroids*	Glucagon
Growth hormone*	Epinephrine
	Insulin antagonists (pituitary, adrenal)
	Diseases, i.e., thyrotoxicosis, cirrhosis of liver, uncontrolled diabetes

* See text for explanation.

Other substances known to affect glycogen levels include epinephrine and glucagon or alpha cell hormone of the pancreas. Sutherland[29] demonstrated *in vitro* that both of these substances, which *in vivo* raise the blood sugar and deplete liver and muscle glycogen, act upon phosphorylase and maintain the enzyme in its active form, phosphorylase-a. This increased glycogenolytic action, as opposed to the glycogenic action of phosphorylase, has not yet been explained. Further, although the role of epinephrine in the human subject is well established, that of glucagon is not. Some investigators believe that glucagon is a basic regulating hormone concerned with the maintenance of the blood sugar and McQuarrie has suggested that a glucagon deficiency exists in certain cases of hyperinsulinism.[30]

Hastings and his coworkers have been instrumental in pointing out the importance of electrolyte concentrations in processes of glycogen synthesis. He has shown that in order for the isolated liver tissue to synthesize glycogen, the tissue must be suspended in a medium containing high concentrations of potassium.[31] Muscle, on the other hand, will not synthesize glycogen in the presence of relatively great concentrations of potassium.[32] The significance of these observations in the intact animal is not yet clear, although it may be postulated that alterations in serum and tissue potassium, sodium and phosphate may well affect glycogen synthesis *in vivo*.

In general it may be said that the absence or decrease in activity of the glycogen-synthesizing enzymes could result in low glycogen levels while a decrease in the activity of the degrading enzymes could result in high concentrations in tissues. It is also conceivable that disproportionately increased activity of one group of enzymes as opposed to the others could influence the level of glycogen.

Those factors, then, which tend to accelerate the uptake of glucose by tissues produce increased levels of glycogen, while those depressing glucose uptake produce the reverse effect. (Table II.) Substances such as epinephrine and glucagon may conceivably influence glycogen levels by being present in greater or lesser quantities than normal. Finally, the activity of the enzymes concerned with glycogen metabolism may affect the glycogen levels. At the present time it is not known by what specific mechanism these factors regulate cellular glycogen levels but it is not farfetched to postulate that they do so by altering the enzymatic activity.

Before concluding this section it should be mentioned that certain disease processes appear to be associated with altered glycogen levels. Patients with thyrotoxicosis and cirrhosis of the liver tend to have low liver glycogen levels, the first presumably based on excessively rapid utilization, the second presumably associated with overall enzymatic deficiencies.[18] In diabetes, although liver glycogen may be low, one often sees increased deposits of glycogen in the kidneys and in the cardiac muscle[33] as well as in the beta cells of the pancreatic islets.[34] The basis for these deposits is not known although some investigators have suggested that hyperglycemia secondary to inadequate control of the disease may play a part. Finally it is of interest that the normal infant heart contains as much or more glycogen than many cases of cardiomegalic glycogen disease.[35]

Having considered the overall picture of the complexities of glycogen metabolism in the normal individual, the remainder of this paper will be concerned with the disorders of glycogen metabolism.

GLYCOGEN STORAGE DISEASE

Glycogen storage disease is a generic term applied to a group of congenital and familial disorders characterized by the deposition of abnormally large amounts of glycogen in the tissues. These diseases have been classified into four types on the basis of clinical, pathologic, and biochemical characteristics: Type I, von Gierke's disease or hepatorenal glycogenosis; Type II, glycogen storage disease of the heart; Type III, diffuse glycogenosis with cirrhosis of the liver; and Type IV, glycogen storage disease of liver and muscle.

This classification is based in part on that of Andersen[36] and in part on that of Cori.[18] For detailed and critical descriptions of these entities, the reader is referred to the papers of van Creveld,[37] Mason and Andersen,[38] Langewisch and Bigler,[39] di Sant'Agnese,[40,41] and Forbes,[42] as well as the standard textbooks of pediatrics.

Type I: von Gierke's Disease

Clinical Findings. This syndrome usually has its onset at birth or in early infancy. Often the only abnormality is the existence of an asymptomatic hepatomegaly. History of a sibling affected with this disorder may be the first clue to diagnosis. Symptoms may progress from anorexia, weight loss, abdominal enlargement, vomiting, and non-specific complaints to hypoglycemia, convulsions and coma. On physical examination there is found retardation of growth (occasionally dwarfism), obesity giving the child a "doll-like" appearance, hepatomegaly and palpable kidneys. Laboratory examination is marked by acetonuria, hypoglycemia, hyperlipemia, increased blood glycogen levels,[43] inadequate response to epinephrine, impaired glucose-tolerance, decreased serum phosphate and no response to glucagon.[44] The course is usually short but depends on the degree of involvement. Some patients live to adolescence. Death is usually due to intercurrent infection. Treatment consists in frequent high protein feedings and ACTH or cortisone[45] in an effort to control hypoglycemia. Sodium lactate is given for the acidosis which is often marked.[46]

Pathologic Findings. Andersen[36] has reported observations noted at autopsy on a patient with von Gierke's disease who lived for over two months, ultimately succumbing to a respiratory infection of two days' duration. The liver was massively enlarged, weighing 770 gm. (normal, 140 gm.), and the kidneys were moderately enlarged, with a combined weight of 58 gm. (normal, 40 gm.). Aside from pneumonia, no other abnormalities were observed upon gross examination. On microscopic examination, however, both the liver cells and the cells of the convoluted renal tubules were heavily loaded with glycogen; in addition, the liver cells contained an abundance of fat. Best's stain confirmed the large deposits of glycogen in the liver and kidneys and also revealed small amounts of glycogen in the heart, tongue and skeletal muscle.

Biochemical Findings. This disorder is characterized by hepatorenal deposits of metabolically unavailable glycogen. The unavailability of glycogen is attested to by the hypoglycemia and the absence of response to epinephrine. Ketosis and hyperlipemia are consistent with a shift to fat metabolism and reflect a carbohydrate-starved organism.

In an analysis of the defect several possibilities present themselves. Glycogen may be unavailable because of (1) a structural abnormality, which prevents the normal enzymes from degrading it, (2) a deficiency of the glycolytic enzymes or (3) an abnormality in the hormones or factors which regulate glycogen levels.

With regard to the structure of this glycogen it was known, following the experiments of Schoenheimer, that normal liver mince could degrade it, but it could not be degraded in the livers of patients with the disease. This suggested that its configuration was normal. In an analysis of the structure of the glycogen obtained from ten cases of this disease, G. T. Cori showed that the structure did not differ from that of normal. Phosphorylase degraded the molecule from 30 to 42 per cent while in the normal the values were 25 to 41 per cent. Further, the percentage of branch points was found to be 6.7 to 9.5 per cent while in the normal it was 7.1 to 8.4 per cent.[10]

In approaching the second possibility, that of enzymatic defect, the Coris reasoned that the glucose-6-phosphatase was most probably at fault. This was based on the fact that liver and kidney rather than muscle were involved by the disease and that the glucose-6-phosphatase is present in the former two organs and not in muscle. In seven cases the glucose-6-phosphatase activity of liver was demonstrated to be extremely low.[47] Activity of the enzyme in kidney

was also low in two cases. No evidence of significant inhibitors of this enzyme in these livers could be found. In five other older patients with a milder form of the disease, the phosphatase was only slightly depressed and in one case was within the normal range. Although this deficiency in glucose-6-phosphatase is an important factor in the mechanism of the glycogen storage, some question may remain as to whether it is the sole cause of this type of storage disease. It is possible that the low serum phosphate reported in these cases may also contribute to glycogen storage.

Type II: Glycogen Storage Disease of the Heart

Clinical Findings. The onset of this disease occurs early in infancy and is marked by feeding difficulties, intermittent cyanosis, and dyspnea. Cardiac failure, listlessness, muscular weakness, neurologic abnormalities and striking enlargement of the tongue may be noted. On physical examination, the diagnosis may be confused with hypothyroidism,[48,49] mongolism, or amyotonia congenita because of the extreme muscle hypotonia.[50] The heart is usually enlarged, and systolic murmurs are present in some cases. Laboratory studies reveal no abnormalities of carbohydrate metabolism. The cardiac silhouette on x-ray tends to be globular. Electrocardiogram reveals inverted T waves, left axis deviation and S-T depression with a normal P-R interval. The course is short with death resulting from infection and heart failure during the first eight months. No treatment is known.

Pathologic Findings. Pathologic findings in cardiomegalic glycogen disease have been summarized by di Sant'Agnese et al.,[41] who have reviewed fourteen cases previously reported in the literature. The outstanding findings revealed upon gross examination were in the heart, which in every case was strikingly enlarged, weighing in some instances 5 to 6 times the normal for the age of the patient.

Histologically, the marked infiltration of the myocardium with glycogen yields a distinctive microscopic picture, lending a "lacework" appearance to the fibers, each fiber appearing as a hollow cylinder surrounded by a thin, delicate cytoplasm with the nucleus lying free in the center. These alterations in structure are often so marked as to make recognition of the myocardial tissue difficult.

In six of the fourteen cases, glycogen was noted in the skeletal muscles. The tongue was consistently and markedly affected, the diaphragm less so, while the musculature of the neck, trunk and extremities contained variable amounts. Glycogen deposits were also observed in smooth muscle, the cells of the reticuloendothelial system, the kidney, the liver and in the reticulum cells of the spleen, lymph nodes, bone marrow and thymus.

Epithelial cells in which glycogen deposits have been noted are the mucus glands of the gastrointestinal tract, the acinar, ductal and islet cells of the pancreas, the cortical and medullary cells of the adrenals and, finally, the epithelial cells of the hair follicles. The ganglion cells and central nervous system may also be involved. There is no apparent reaction of the tissues to the accumulation of glycogen.[50]

Biochemical Findings. In this disorder of cardiac and generalized glycogenosis, no abnormalities of carbohydrate metabolism are found. This implies that the glycogen is available for utilization by the body. The Coris found that both the structure of the glycogen and the glucose-6-phosphatase activity of the liver and kidney were within normal limits in one carefully studied case. Since this disease affects chiefly muscle, one would not have anticipated a defect in the phosphatase system. At the present time no explanation of the abnormality is available.

Type III: Diffuse Glycogenosis with Hepatic Cirrhosis

Clinical Findings. Symptoms may appear at any time from late infancy to early childhood. The complaints are referable to hepatic involvement, with edema and abdominal swelling and occasionally bleeding tendencies. Upon physical examination hepatosplenomegaly, ascites, jaundice and anemia may be evident. The laboratory confirms abnormal liver functions (cephalin flocculation, thymol, bromsulfalein retention, low serum albumin and elevated serum globulins, bilirubinemia). The blood sugar is normal and no acidosis is present; response to epinephrine may be moderate and delayed. The glucose tolerance test may show a moderate rise and a slow fall of the blood sugar. The course is variable and death may occur between the ages of one to ten years.[36] Treatment is directed to the liver disease, although apparently it is not effective.

Pathologic Findings. Andersen has reported observations noted at autopsy of a seventeen month old child who died of glycogenosis with

hepatic cirrhosis; a previous sibling had died with hepatosplenomegaly and von Gierke's disease, the latter being diagnosed posthumously.

The liver weighed 560 gm. (normal, 330 gm.) and had a finely nodular surface. The spleen was also enlarged. Microscopic examination revealed a diffuse, finely nodular cirrhosis with large glycogen deposits in the liver cells; in the thickened, fibrotic portal areas were proliferating bile ducts, isolated liver cells and diffuse infiltration with round cells and polymorphs. In the spleen there were accumulations of what appeared to be reticulum cells loaded with glycogen; similar accumulations of phagocytic cells loaded with glycogen were found in the lymph nodes, the lymph follicles of the intestine and the intestinal mucosa; in all areas these phagocytic cells were accompanied by a mild fibrous reaction. Small amounts of glycogen were found in diaphragmatic muscle fibers but none were found in the kidneys.

TABLE III

SUMMARY OF GLYCOGEN STORAGE DISEASES

Type	Organs Affected	Age		Hypoglycemia, Ketosis, Hyperlipemia	Epinephrine Response	Glycogen Structure	Enzymatic Alterations
		Onset	Death				
I	Liver; kidney	Neonatal; infancy	Varies with severity	++++	0–++	Normal	Decreased to absent glucose-6-phosphatase
II	Heart muscle, tongue, brain	Neonatal; infancy	Early	0	Normal	Normal	None found
III	Liver (cirrhosis); reticuloendothelial system	Late infancy	1–10 yr.	0	++	Abnormal: excessively long outer branches	Probably decreased brancher activity
IV	Liver; muscle	Late infancy	?	++	+	Abnormal: very short outer branches	Probably decreased debrancher activity

Biochemical Findings. The pathologic findings in this variety of glycogen disease suggest that glycogen behaves as a foreign body to which there is tissue reaction, that is, cirrhosis of the liver and fibrosis surrounding the deposits of glycogen. This finding is totally consistent with the striking alteration in structure of this glycogen reported by Cori.[18] End group analysis revealed branch points of 4.7 per cent, phosphorylase degradation 50 per cent, average outer chain length 14.7 residues, and inner chain length 6.5. Thus there were fewer branch points and significantly longer chains. These findings suggest a deficiency of the brancher enzyme. The glycogen formed resembles amylopectin, the branched component of starch. Certain of the physical properties are consistent with this view and are markedly different from normal glycogens (x-ray diffraction diagram, solubility properties and absorption maxima after the development of the iodine color).

Type IV: Glycogen Storage of Liver and Muscle

Clinical Findings. This appears to be a very rare disorder. Only one case thus far recorded* was noted by Forbes.[42] In this case, there was no familial history of glycogen disease. Abdominal enlargement was first noted at the age of one year. Physical examination revealed only hepatomegaly. Mild hypoglycemia and acetonuria were noted. There was no bromsulfalein retention. A mild normochromic anemia was present. The patient was followed carefully and developed normally in every way. At twelve years of age, hepatomegaly was more striking and

* An additional case has been diagnosed by Dr. Alexis F. Hartmann at the Children's Hospital in St. Louis. Hypoglycemia, hyperlipemia and hepatomegaly were noted. The patient died at thirteen months of age with glycogen storage in the liver, heart and muscle. Glycogen structure showed findings similar to that of Forbes' case.

abdominal veins were prominent. Fasting ketonuria was noted. Cephalin flocculation was three plus, and marked bromsulfalein retention was found. The response to epinephrine was present but less than normal. It was of interest that over a ten-year period of observation the fasting blood sugar levels tended to rise and the lipids to fall. The patient, now thirteen years of age, is still living and does not appear chronically ill.

Pathologic Findings. Pathologic findings in this case have been limited to biopsy specimens taken at age twelve and a half. The liver specimens revealed parenchymal cells packed with glycogen, as identified with Best's stain; aside from this and some increase in periportal connective tissue, the liver was otherwise not remarkable. Routine hematoxylin and eosin sections of skeletal muscle revealed no abnormalities.

Biochemical Findings. High levels of glycogen were noted in muscle and liver biopsy specimens from this patient. The combination of glycogen storage in muscle and liver with a definite but abnormally small response to epinephrine suggests (1) that the glycogen is only partially available and (2) that the defect is probably unrelated to the glucose-6-phosphatase. Structural analysis of this glycogen was particularly interesting. Liver and muscle, respectively, showed end groups of 10.8 and 13.1 per cent and phosphorylase degradation of 12.2 and 2.6 per cent. These findings indicate an enormous number of branches and very short outer chains with the molecule essentially similar to limit dextrin. Cori suggests that there is a deficiency of debranching enzyme while phosphorylase is apparently normal. In this way the outer tier residues are readily released and rebuilt but the inner core is unavailable. This could explain glycogen storage and partial response to epinephrine.

A summary of the salient features of these four types of storage disease may be found in Table III.

SUMMARY

The field of carbohydrate chemistry and metabolism has advanced tremendously over the past twenty-five years. Elucidation of the enzymatic steps involved in the synthesis and degradation of glycogen has been one of the most important contributions. This has provided not only an understanding of glycogen metabolism in the normal individual, but has permitted an evaluation of glycogen storage diseases. Based on the clinical, biochemical, and pathologic data described, these diseases, once considered a single entity, have been classified into four types. Fundamental distinctions among these diseases have been demonstrated to reside in a variety of enzymatic defects in glycogen metabolism, resulting in increased tissue glycogen concentrations in all cases and in abnormal glycogen structure in some cases.

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Conference on Therapy

Choice of Therapy in Intestinal Parasitic Disease

These are stenographic reports, which have been edited, of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

Dr. George Reader: The choice of therapy in intestinal parasitic diseases is the subject of this conference. The discussion will be opened by Dr. Kean.

Dr. B. H. Kean: We might modify the title a bit by saying that we will discuss only the more common intestinal parasitic diseases. There are a great many intestinal parasites but if we exclude about ten of the more exotic varieties, limiting ourselves only to those which we might encounter in the New York City area, we are left with about fifteen diseases. These include amebiasis, two flagellate diarrheas, five helminthic infections, four tapeworm diseases and schistosomiasis which is caused by a fluke. This is still an ambitious undertaking for one session and we shall try to deal only with as many as space will permit.

I should like to say at the outset that much that is written about the results of various treatments should be regarded with suspicion. It seems to be unusual to find an initial evaluation presenting the facts. For example, for many years we believed we knew how to treat ascariasis. We used to speak of cures in about 90 per cent of the cases and that is what one finds in almost any textbook. At the last meeting of the American Society of Tropical Medicine eight different persons from various parts of the world agreed that we are far from knowing how to treat Ascaris lumbricoides and that currently the cure rate is only about 35 per cent.

The situation in the case of pinworm is well known, for there is no ideal therapy for this disease. We shall discuss pinworm in more detail later.

Let us for a moment consider the most important of this group of diseases, that caused by Endamoeba histolytica or intestinal amebiasis. Even if we do not consider the archaic drugs which clutter up the field and mention only those currently in use, the list is large; emetine, various arsenicals like carbarsone,® milibis® and balarsen,® the halogenated hydroxyquinolines like diodoquin,® chiniofon, yatren® and vioform, a half dozen antibiotics, and some others which do not come to mind at this moment. Five or six years ago, when bacitracin became available, it appeared that the cure for amebiasis had been found. That illusion lasted only a year, for the cure rate dropped to about 20 per cent. Aureomycin was the next drug to appear, with an initial cure rate approximating 95 per cent. These rates have now dropped to about 30 to 50 per cent. The initial reports in the case of terramycin® were very optimistic. There was one report that sixty people were treated with terramycin, 2 gm. a day for about ten days, that the cure rate was 100 per cent, and that there were no toxic symptoms, diarrhea, nausea or complaints. It is my experience that you cannot give 2 gm. of terramycin a day to sixty patients without receiving complaints. Terramycin is still being used and is probably the best single drug for amebiasis but the ultimate evaluation of its efficiency requires an open mind. Fumagillin is another of the special cures for amebiasis. By the time the drug appeared on the market the cure rate was dropping from 90 per cent to 75 per cent; one can predict that in a year or so the cure rate will be still lower. It should be noted that terramycin affects bacteria to a much greater extent than does fumagillin. Tetracycline is being evaluated at the present time. Chlo-

roquine diphosphate might also be mentioned; it is virtually useless for intestinal amebiasis but very important for the treatment of hepatic amebiasis, in conjunction with emetine.

Emetine is, of course, used for both the intestinal and hepatic forms of amebiasis. There is something strange about this drug. It is the only one among all of the drugs previously mentioned that is a true amebicide, that is, it kills amebas in dilutions which may reasonably be expected to prevail with therapeutic doses. It is, of course, easy enough to set up test tube culture experiments and demonstrate amebicidal actions with terramycin or other drugs, but so far as we know none of these, with the sole exception of emetine, kills amebas in therapeutically relevant dilutions. Emetine is potent against the amebas in dilutions of 1:5,000,000 and it kills amebas in dilutions of 1:1,000,000. There is, of course, the difficulty that emetine is a fairly toxic substance. Strangely enough, in spite of its high amebicidal action, emetine alone never cures intestinal amebiasis. I do not have an adequate explanation for this phenomenon. Used in conjunction with certain other preparations, emetine is, of course, extremely effective in bringing about a cure.

Among the more popular members of the arsenical group, namely, carbarsone, balarsen and milibis, there is very little choice. We prefer carbarsone. There has been a great deal of experience with it over the years, and its toxicity is reasonably low for an arsenical compound. Some of you may remember the report by Anderson about two years ago in which he described the use of thioarsenites for amebiasis. This material has been found to be too toxic for clinical use and is not commercially available.

There is relatively little to choose from among the preparations of halogenated hydroxyquinolines. We prefer diodoquin. It seems to be the most popular among this group of materials. For many years it was the drug of choice in New Orleans where it cured about 95 per cent of cases of amebiasis. This hopeful report was followed by other reports from England which declared the drug to be almost worthless. The United States Navy refused to include diodoquin in its list of necessary drugs, mainly on the basis of the British experience. In recent years the experience in New Orleans seems also to show a falling off of the cure rate. At the present time it is probably closer to 50 per cent, although most of the reports still refer to from 60 to 80 per cent.

Since none of these drugs is entirely satisfactory, we pursue the plan of using several drugs, stretching the treatment over long periods of time. One plan we use in the treatment of amebiasis is to administer 1 gr. of emetine (65 mg.) intramuscularly daily for five days. It may be mentioned parenthetically that in the case of the five-day therapy electrocardiographic control is not necessary. It is desirable to use electrocardiographic checks when the treatment is carried on over a longer period of time, say ten days, as in the case of hepatic amebiasis or in older persons. With a shorter period of treatment some changes in the T waves may appear but they are unimportant from the practical standpoint; and if there has been no untoward reaction to the first dose of emetine, it is unlikely that anything serious will occur during the first five days. This is not true, however, with longer treatment. Simultaneously with the emetine we start carbarsone, 1 gm. daily, continued for ten days, one 0.25 gm. tablet being given four times daily. This is then followed by a course of terramycin, 1.5 gm. the first day and 1 gm. daily thereafter for a week. If the patient seems able to tolerate more terramycin, it may be given for ten days. This schedule constitutes our initial effort to cure a patient of amebiasis. We expect a cure with this method in about 90 per cent of the cases. If follow-up reveals that the parasite has returned, the whole course of treatment is repeated, adding a fifteen- or twenty-day course of diodoquin. We usually give 2.5 gm. daily in divided doses to an adult. This should result in the cure of a fair number of the 10 per cent failures. There is still a small residual group which is resistant to cure and which constitutes quite a problem.

DR. HARRY GOLD: Would your general formula of treatment apply to the asymptomatic form of amebiasis as well?

DR. KEAN: There has been some question and considerable debate about that over the years. Now, with the known danger of hepatic amebiasis, and with fuller recognition of the importance of the public health aspects of the disease, the debate is almost over. Consider for a moment what one means by a case of asymptomatic amebiasis. This is a patient who believes that he is perfectly well and may even regret that he has had the misfortune of having had his stool examined, as the result of which a parasite was found. The plan of therapy which I outlined might be accepted readily as appropriate

for acute amebic dysentery when it is necessary to alleviate the patient's symptoms. There may be a doubt, however, as to whether one is justified in using this heroic treatment in a person who seems perfectly well. Experience indicates that many people with so-called asymptomatic amebiasis who think they are well are not really in perfect health but are able to recognize this fact only when the so-called asymptomatic disease is cured. It is very much like a patient with low-grade anemia who does not know how well he can be until the anemia is cured. All patients with amebiasis should be treated. There is still some question as to whether the treatment should be as thorough in these cases as in the symptomatic ones. It is our inclination to treat them in the same way. We warn the patient that he may feel worse during the treatment but that he may anticipate feeling better after treatment than before.

DR. READER: We might ask if there are any questions about amebiasis before we go on to some of the other parasites. Dr. Almy, do you have any comment on the treatment of amebiasis?

DR. THOMAS P. ALMY: I was wondering about the feasibility of giving five daily injections of emetine to ambulatory patients who do not admit having any symptoms. Are you not forced at times to modify the schedule and, if so, just how do you do that?

DR. KEAN: You have called attention to a most important point, especially applicable to treatment in clinics of large numbers of patients. There we are inclined to eliminate emetine from the program and carry out only the other parts of the schedule. The pain of an injection of emetine is sometimes considerable. One cannot use a drug with the potential toxicity of emetine in hundreds of individuals in clinic populations without occasionally getting into some difficulty. We are less apt to encounter this trouble in the case of the more individualized care of private patients, and in such cases we are apt to carry through the full regimen of treatment. I would be interested in knowing what you think about this, Dr. Almy. Do you prefer to use one drug at a time and see how the patients get on, and, if they are not cured, then to turn to another drug or do you prefer to use several measures at the same time?

DR. ALMY: I have been using only one drug but am perfectly happy to use two or three. I would be very much interested in a convincing demonstration of the differences in the results.

DR. READER: Dr. LeMaistre, I wonder whether you would have any idea as to why terramycin is so effective and aureomycin is not?

DR. CHARLES A. LEMAISTRE: I am inclined to think that the difference between the two is accentuated by studies and data that are not of equal quality. On reviewing the data on aureomycin a few months ago I was impressed with the fact that the evaluation of this drug has not been as careful, extensive and thorough as it has been in the case of terramycin. It may well turn out that the two are not materially different, but at the present time, as Dr. Kean knows, I personally prefer terramycin.

DR. ALMY: I was rather cast down to hear Dr. Kean imply that an ancient explanation is probably not correct. It used to be said that emetine is ineffective against the cyst form of the ameba, and since the cyst form could not be eradicated from the lumen of the intestine it reinvaded the bowel and in that way prevented a cure. Is that now thought to be incorrect?

DR. KEAN: One cannot be certain whether it is or not. You all remember that amebiasis is usually acquired by drinking contaminated water. If the trophozoite is ingested in this way no harm is done because it does not survive the gastric barrier, even though this is the form of the ameba that is so dangerous to the host. On the other hand, ingestion of the cyst form gives rise to the disease because the cyst passes the stomach unharmed and in the intestine divides, yielding trophozoites. These trophozoites invade the mucosa, destroy portions of the submucosa, and lead to impairment of the blood supply with eventual ulceration of the mucous membrane. The question that has come up is this: Is the conversion from trophozoite to cyst a reversible process in the same patient? A certain number of trophozoites, instead of invading tissue, round up and form cysts which may be passed in the stool. Can these newly formed cysts divide and release trophozoites without crossing the gastric barrier of a new host? There is no final answer.

DR. READER: I wonder if Dr. Grace would care to express an opinion as to why some people develop acute dysentery from the ameba and others carry the organism without developing the disease? Do you believe there is something in the nature of bowel function which determines the course?

DR. WILLIAM J. GRACE: There are some observations that indicate a relationship between the character of the intestinal tract and the

susceptibility to symptoms in amebiasis. We have had a few patients in whom symptoms of amebiasis developed only during periods of stress. It seems to be a fact that the condition of the mucosa of the gastrointestinal tract determines the ability of organisms to penetrate. Norris and Rappaport made some experiments along that line. They gave an irritant enema of turpentine. Under ordinary circumstances 10 per cent of the animals could be infected, whereas under these unusual conditions the infection rate went up to 50 per cent. The observations that we have on changes in the mucous membrane under the reaction of stress indicate that the membrane becomes more fragile, and that some alteration in mucous formation takes place. It is my notion that this is the kind of condition most likely to lead to infection by an organism which otherwise might prove innocuous.

DR. READER: Do you have any opinions on this point, Dr. Kean?

DR. KEAN: Attempts have been made to increase the rate of infectivity in experimental work by irritating the intestinal tract with croton oil and there is some evidence that the rate of infectivity may be increased in this way. You might be interested in the relationship between mucous colitis and amebic dysentery. This is not directly an answer to Dr. Reader's question but is related to it in that it has to do with the state of the mucous membrane and its susceptibility to infection. The matter stems from some army experience. A number of individuals are in Veterans' Hospitals or are drawing disability pay who have been diagnosed as having amebiasis but who actually have ulcerative colitis. What happened in the past was that the patient came in with symptoms of colitis, amebas were found and thorough treatment instituted. Later recurrence occurred and was called amebiasis. The patient was again treated and later had another recurrence. This last episode which was called a recurrence was no longer, however, amebiasis but ulcerative colitis. Now the stool no longer showed parasites. Does this mean that amebiasis produced the picture of ulcerative colitis? Does this indicate that the patient had potential susceptibility to ulcerative colitis and that an appropriate trigger brought it out, in this case the attack of amebiasis? There are those who believe that in ulcerative colitis bacillary dysentery is the trigger. One must, of course, consider the fact that if 10 per cent of the population has amebiasis there are a certain number of cases in which the two diseases overlap.

DR. GRACE: We have seen a few cases in our clinic of the kind that Dr. Kean has described, namely, individuals who showed all the characteristics of ulcerative colitis and in whom the ameba was found in the stool. It was my belief that the ameba was just an incidental finding.

VISITOR: I do not think you said very much about the hepatic abscess. You did mention ten days of treatment with emetine in the case of hepatic abscess. Could we hear more about this?

DR. KEAN: The reason I did not go into it is that the subject of this conference is the treatment of intestinal parasites. We believe the evidence is fairly strong that the only hepatic lesion in amebiasis is a localized abscess and that amebiasis does not cause a specific diffuse hepatitis. This view is held despite the numerous articles to the contrary. Any enlargement of the liver, tenderness and changes in liver function tests which are thought by some to be caused by diffuse amebic hepatitis are manifestations of non-specific changes in the liver seen in any ulceration of the intestinal tract. For the treatment of amebic abscess there are two effective drugs, one is emetine and the other chloroquine diphosphate. Emetine has been the standard drug for many years. A course of treatment is ten daily intramuscular injections of 1 gr. each (65 mg.). After a rest period of three or four weeks the course of treatment may be repeated. For the past five years, or possibly a little longer, chloroquine diphosphate, introduced by Conan, has been in use. Employment of this drug is based on knowledge derived from studies of malaria, which showed that chloroquine was concentrated in the liver. It seems to be just as effective as emetine. The dosage schedule has not been completely worked out. It appears that 1 gm. the first day and 0.5 gm. daily for the next two weeks is a reasonably satisfactory program. It is a cumulative drug but its toxicity is not high. At the present time we do not yet have the courage to depend upon this drug alone and so we use emetine and chloroquine in alternating courses. Dr. Conan has had very good results using chloroquine alone.

DR. GOLD: Has terramycin any value in amebic abscess?

DR. KEAN: Yes and no. Terramycin sometimes brings about a spectacular drop in the temperature and, in the signs of intoxication,

chills and general malaise. Approximately one-third of patients with amebic abscess develop a secondary infection and the invaders are usually the colon bacilli. Terramycin produces its spectacular effect by acting on these, but it will not destroy the amebas and hence this striking change in the picture is only a temporary one. There is no objection to using terramycin in conjunction with emetine and chloroquine.

DR. READER: Perhaps we should go on to the next group. Would you say a word about the flagellates, Dr. Kean?

DR. KEAN: I think we can dispose of these very quickly. Giardia lamblia is treated by a standard therapy that is effective. There is no alternative. The drug is one which was used in malaria, quinacrine hydrochloride or atabrine®. In the usual schedule one gives five tablets of 0.1 gm. each the first day (that is, 0.5 gm.) and then three tablets or 0.3 gm. in divided doses daily for a week or ten days. The cure rate is about 90 per cent. After a week or ten days the course can be repeated. There is some debate on the question as to whether G. lamblia causes disease. There is fairly good evidence, however, that about half of the individuals who have this parasite are subject to bouts of diarrhea, symptoms of dyspepsia, atypical gallbladder disease, peptic ulcer, or so-called gastric neurosis. I shall not forget the aged dowager who developed severe colitis late in life. It was believed that she had a malignancy. She was ill for about six or eight months but would not go to the hospital and would not allow herself to be thoroughly examined. It was finally decided to try to do a barium enema in her home. All the equipment was brought there and two very competent radiologists made the examination. No malignancy could be demonstrated at that time. About six more months elapsed without results, when someone thought it might be a good idea to examine the stool. G. lamblia were found in great numbers. On the third day of quinacrine therapy the disease was brought under control. This is an exaggerated case but it helps to point out something which is worth stressing. It is disturbing to contemplate how extensive a medical work-up will be done sometimes before a stool examination is made. Fortunately, that is not so in this institution.

We might now go on to the subject of tapeworms. I like to talk about this because there has been some advance in the treatment of these worms in the last few years. The classic drug in the treatment of tapeworm is oleoresin of aspidium. It was used by Theophrastis in 300 B.C. and it has been a very effective agent against the tapeworm. However, it has a fairly high order of toxicity and has been largely replaced by quinacrine hydrochloride (atabrine) as the drug of choice. In view of the effectiveness of quinacrine and its much lower toxicity, as well as its applicability to all the common types of tapeworm, it would in these days be difficult to defend the use of the older remedy, oleoresin of aspidium.

The mode of administration of these drugs is a decisive factor. The parasite is attached by a tiny, hardly visible head to the mucous membrane of the duodenum. The problem is to get a high enough concentration of the drug to act at the site to which this head is attached. Neither of these drugs actually kills the parasite. They so affect the nervous system of the parasite that the head releases its hold on the mucous membrane. Thus the entire parasite with its head moves past the duodenum into the small intestine and beyond into the large bowel, where it no longer can take hold. The medication should be administered at a time when the intestinal tract is as empty as possible. The patient is instructed to have anything he wants except alcohol until noon. If possible it is best to skip dinner or supper. If he then takes a saline cathartic that night, we may presume that the intestinal tract or at least the upper portion of it is reasonably empty by morning. The medication is given in the morning instead of breakfast. There are those who give quinacrine in tablet form by mouth. The patient swallows a tablet every two minutes until all ten have been taken, making a dose of 1 gm. The drug is quite irritating to the gastric mucosa and frequently a good portion of the dose is regurgitated. The cure rate by this method is only about 70 per cent.

We prefer the method of transduodenal intubation for administering the medication. A duodenal tube is passed. It is possible to control its position by means of the fluoroscope but that is not necessary. If the tube is down to a level where a little bile can be aspirated, we can assume we are in the appropriate region, although it may not be actually in the duodenum. The quinacrine is then introduced into the tube. Two hours later the patient receives another dose of magnesium or sodium sulfate. The batting average by this technic is quite high, the

cure rate being about 90 per cent. On a second trial by the same procedure one is likely to get almost every case. We have recently seen five or six cases in which oral administration of the drug failed but direct introduction of the quinacrine into the duodenum produced a prompt cure. This is logical because by the method of transduodenal intubation a high concentration of the drug is brought directly to the point where it is needed and none of it is lost through vomiting. There is a practical point about the preparation of the quinacrine which is worth mentioning. The drug is relatively insoluble in water and one may spend the entire morning getting it to disintegrate. It is our practice to put the ten tablets into water in a medicine glass and allow them to soak over night to give them sufficient time to disintegrate. This results in a partial solution and suspension which can be fairly easily introduced into the duodenal tube.

If for any reason you do not wish to use quinacrine, oleoresin of aspidium can be applied in the same way through the tube. Mix 6 to 8 gm. of the freshly prepared drug with about 30 cc. of acacia and 30 cc. of a solution of magnesium sulfate. This rather vile looking concoction is put down the duodenal tube. The results are about as good with this drug as with quinacrine but because of its toxicity one is put in the position of having to defend the use of aspidium.

DR. GOLD: This is, then, really a one-dose treatment, is it not?

DR. KEAN: Yes, a one-dose treatment.

DR. ALMY: Can any other saline cathartic be used or is magnesium sulfate still considered the best?

DR. KEAN: Magnesium or sodium sulfate is usually advocated.

DR. GOLD: Sodium phosphate is much more pleasant. Would it be all right to use that instead? Taste, of course, does not matter when the material is introduced into the duodenal tube.

DR. KEAN: I see no reason why phosphate of soda would not do just as well.

DR. ALMY: Have you ever seen any toxicity from magnesium sulfate?

DR. KEAN: It may well have occurred unnoticed. Of course, the dose we use is not much greater than patients have been accustomed to taking in the form of Epsom salts or Glauber's salts. I do not imagine an important degree of poisoning is very common.

DR. READER: Are there any other questions? Dr. Gold, have you one?

DR. GOLD: I gained the impression from what Dr. Kean said at the beginning that 90 per cent cure rates reported in initial experiences with various drugs in the treatment of parasitic diseases usually dropped to about one-third with larger experience. Now Dr. Kean points to a method of treatment which involves the use of three agents in a particular regimen and he obtains cure rates of 90 per cent or so. Is there a chance that the new treatment may also let us down and in time show much lower cure rates? I mention this point not because I have any reason for doubting the superiority of the new method but because of the fact that it seems to be characteristic of the problem of therapy in the parasitic diseases that initial responses to therapeutic agents give rise to the appearance of a cure which turns out to be more in the nature of some sort of temporary suppression rather than a cure. That kind of phenomenon could operate through all kinds of treatments and produce similarly misleading results.

DR. KEAN: It is quite possible that my figures for cure rates may be reduced in three or four years. I doubt that it is likely to fall in the case of the treatment of tapeworm because the proof of the cure is the finding of the head in the stool. That leaves no room for dispute.

DR. READER: It would be nice to hear from you now, Dr. Kean, on the subject of pinworms.

DR. KEAN: There are a great many drugs which have been used in the treatment of pinworm and it has not been easy to ascertain their usefulness. Pinworm presents a very special problem. There is no cycle that is simpler than the pinworm cycle. The child or adult consumes the eggs and the adult worms develop in the large bowel. The female migrates usually at night to the perianal region and deposits its eggs there. The patient scratches the anus, contaminates the fingers with eggs, and then introduces the eggs into the mouth, thus completing the cycle. There has been a good deal of discussion about the wide distribution of pinworm eggs. They have been found in strange places, on chandeliers and under carpets, but if those locations were of any importance we would probably all have pinworm disease. The factor that keeps the disease going is the scratching of the anus and the subsequent introduction of the eggs into the mouth. Anus scratching is a very common practice. It is done by about one-

third of children and many adults. If you were to paint the perianal region with methylene blue you would be surprised to see how often dye will be present on the fingers in the morning. Or dip the fingers in the morning in a culture medium and see how often colon bacilli will grow out.

In order properly to evaluate a therapeutic agent in the treatment of pinworm it is necessary to ascertain first what can be accomplished by stopping the child from scratching at night. If this measure were successful the cure rate for pinworm would approximate 100 per cent. The adult female of the pinworm lives only eight weeks; hence if reinfection can be prevented the disease will be cured in eight weeks. It is difficult to determine the value of drugs in pinworm because studies fail to distinguish the role of drugs and hygienic measures. Both have usually been employed together.

Hygienic measures are the most important part of any regimen of treatment. The first thing to do is to try to control the itching. An antipruritic ointment of one kind or another is applied. For a long time the ointment of ammoniated mercury was used. We prefer a preparation called perazil® ointment which contains an antihistaminic and a surface anesthetic. There must be a great many others that are just as good. We have made use of the seal-in type of pajama, a one-piece garment zippered to the top which can be tied at night. A pair of underpants is also worn. The rear is so sealed that the child must take off the garment in order to use the facilities. Now the child can attempt to scratch as much as he wants. The urge to scratch the anus is irresistible. Dr. Hall photographed children with pinworm disease after having them tied up so as to try to prevent scratching. He found that when the hand could not be brought to the anus, the anus was brought to the hand by a process of bodily contortion which was almost unbelievable.

If, then, the child is sealed in by this method and an ointment is used to allay the itching, the outlook for cure of pinworm disease is, I would say, about 50 per cent. This figure applies to adults as well. I believe that a great many of us have had pinworm disease and have cured ourselves simply by hygienic measures, by washing the hands after anal scratching.

Now, how about the use of drugs? As I have already stated, there are a great many drugs that have been employed. Hexylresorcinol is quite effective but its toxicity is too high for use in a disease so benign. Terramycin, gentian violet and piperazine citrate are the drugs of choice at the present time. The pinworm is a parasite too tough to kill. Terramycin simply deforms the eggs so that a certain percentage lose their viability. We do not know quite how piperazine citrate acts. Gentian violet appears to have some effect on the adult worm as well as on the eggs. What we aim to do is to establish a cycle of biologic attrition in which more of the parasites die off than are acquired over a particular period of time. That seems to be the best that can be done. As in the case of other parasites the cure rates in pinworm disease also vary considerably. Dr. Harold Brown at Columbia obtained cure rates as high as 85 per cent with piperazine citrate. Our own results with this compound are only about 50 per cent. It is easy to understand the higher cure rates in a well planned experiment in which all the details of treatment can be checked and controlled. The cure rate falls off considerably when the drug is used under the more usual clinical conditions. Our practice is to use all three drugs: terramycin for three days, gentian violet for seven to ten days, and piperazine for seven to ten days. We have stopped using diphenan.

DR. GOLD: I wonder what the results would be if one of these drugs were used alone for the longer period of time, I mean the length of time taken for treatment with the three drugs in succession.

DR. KEAN: That is being tested out. It cannot, of course, be done with gentian violet because toxic symptoms appear too early. We are now trying several different time schedules with piperazine. Terramycin has been tried in fairly long treatment periods but that proved unsuccessful because even while the terramycin was being given, the eggs reappeared. Furthermore, in the case of this drug there is also the question of toxicity and expense.

VISITOR: An article appeared last year in the Texas State Medical Journal in which it was mentioned that the cure rate with gentian violet and hexylresorcinol was about 70 per cent, whereas with a regimen of garlic it was over 80 per cent. What do you think about that, Dr. Kean?

DR. KEAN: I think you are referring to the article by Killingsworth and others. Garlic has been used for a long time in Europe. It may well have some effect. I do not know the pharmacology of garlic. Is it inert?

DR. GOLD: There is a good deal of potency in garlic, aside from the odor. It contains toxic sulfides and aldehydes as well as many other substances, and it would not be safe to regard garlic as a placebo in any of these studies. How useful garlic is, however, in any of the conditions for which it has been used, still remains to be shown.

DR. READER: Is there anyone who has any questions he would like to put to Dr. Kean?

VISITOR: What are the doses of these drugs for pinworm?

DR. KEAN: In the case of terramycin 1 gm. a day is given to adults and proportionately lower doses to children for three days. The adult dose of piperazine citrate is 0.5 gm. three times a day for seven to ten days. It is not at all toxic so that the same dose could be used for children but it is usually recommended that children under the age of five receive 0.1 to 0.2 gm. three times a day. The dose of gentian violet for adults is 1 gr. (65 mg.) there times daily. The daily dose for children is $\frac{3}{20}$ gr. (9 mg.) for each year of age. A child of six would receive two tablets three times daily, each tablet containing $\frac{3}{20}$ gr. (9 mg.).

DR. GRACE: What hygienic measures do you recommend for children?

DR. KEAN: A lot depends on the harassed mother. The ideal course would be to wash and iron the pajamas daily. They do not need to be sterilized—washing and ironing are sufficient. We generally compromise and insist only on having the underpants washed and ironed daily, the pajamas twice a week. One hygienic measure which I consider absolutely crucial is the shower in the morning, not at night, because it is in the morning that you wash away the eggs which are deposited during the night. This is not so easy to accomplish for mothers seem to be averse to giving the child a shower in the morning and then exposing him to the elements. If there are several children in the same household, the difficulty of getting this done is compounded. The fact remains that a shower at night, while it may be good for other purposes, is not any good for the treatment of pinworms.

DR. READER: What about enemas?

DR. KEAN: There is considerable demand for enemas in the treatment of pinworm. The mother thinks that something is really being done when a pinworm or two is washed out. The fact is that enemas have never proved successful in curing pinworm no matter what has been put in the solution. There are also psychologic reasons for not giving enemas to a child every night of the week. This consideration might be set aside if only the enemas were effective, but they are not.

SUMMARY

DR. B. B. ROY: Parasitic diseases of the intestine are numerous and present a variety of problems in regard to incidence, clinical types, economic groups in the population and geographic situations. Indeed the problems of treatment envisage more than the choice of a remedy. The most efficacious therapy is not necessarily the one suitable for adoption in a particular area or instance. Considerations include toxicity, ease of administration, cost and length of medication, and the patient's ability to cooperate in a therapeutic regimen. It can hardly be expected to cover the entire field in one session.

Dr. Kean wisely selected for discussion a few of the diseases commonly encountered in the New York City area. However, these are not peculiar to this city but are widely prevalent throughout the world, and this fact has added wider significance to the discussion. This session has been profitable in developing the perspective necessary for an appreciation of the general problems of treatment of parasitic infections of the intestine.

A long list of drugs is available for therapy in intestinal infections, some old, some new. The point was made that reported results of various treatments should be regarded with suspicion, inasmuch as initial evaluation seldom presents the ultimate facts. In intestinal amebiasis, because of unsatisfactory results with individual drugs, the treatment plan discussed includes a combination such as emetine, an antibiotic and an arsenical; additionally, in cases of recurrence, a halogenated hydroxyquinone derivative. Details regarding choice of drugs, dosage, length of medication and related problems were outlined and discussed. There was considerable discussion regarding the course to be adopted in cases of asymptomatic amebiasis. The consensus of the Conference was that in view of the public health aspects of the problem and the potential danger of hepatitis such patients should be treated wherever practicable using the same plan suggested for acute amebic dysentery. It was pointed out that these patients who thought they were in good health felt much better after a

course of therapy. Other items of interest included the comparative efficacy of aureomycin and terramycin, the role of stress in precipitating attacks of amebic infection by inducing changes in intestinal mucosa and the relationship, if any, between amebiasis and ulcerative colitis, as well as the question of whether cysts formed in the intestine of a host can divide and release trophozoites without crossing the gastric barrier of a new host. In hepatic amebiasis the lesion is a localized abscess and not a diffuse hepatitis. Recently chloroquine has shown promising results but perhaps it is not yet safe to use it to the exclusion of emetine. The effect of terramycin, which is sometimes spectacular, is related to eradication of associated bacterial infections, not to any specific action on amebas.

Atabrine, now rarely used as an antimalarial, has recently found two useful applications in the treatment of infections caused by G. lamblia and tapeworm. In the former it is the standard drug. In the latter it is at present preferred to the classic remedy, oleoresin of aspidium. The problem in tapeworm infections is to get a high concentration of the drug to act at the site to which the head of the worm is attached. The mode of administration in this disease is therefore a decisive factor. Details of preparation of the patient, administration of medication and evaluation of the results were fully discussed. In pinworm infection the importance of hygienic measures has been emphasized. Since the life of the female worm is about eight weeks, prevention of reinfection for this period could eradicate the disease by hygienic measures alone. However, it is current practice to combine hygienic measures with drugs. It is noteworthy that enemas, a time-honored favorite, are considered ineffective no matter which drugs may be employed.

Clinico-pathologic Conference

Rheumatic Heart Disease, Auricular Fibrillation, Fever, Hematuria without Anemia, Splenomegaly and Sudden Death

STENOGRAPHIC reports, edited by Albert I. Mendeloff, M.D. and David E. Smith, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

A TWENTY-SEVEN year old white male salesman (No. 108212) was admitted to the Barnes Hospital on June 23, 1954, complaining of severe dyspnea.

The patient had been in good health until the age of nine years when a febrile illness developed characterized chiefly by painful swollen knee joints and two episodes of epistaxis. Diagnoses of acute rheumatic fever and rheumatic heart disease were made at the St. Louis Children's Hospital. He was sent to a children's convalescent home where he remained for two years without apparent symptoms of rheumatic activity. He remained at bed rest for two or three months after returning home.

Despite the knowledge that he had a "bad heart," the patient was able to resume full activity during the next twelve years with only a few restrictions. He finished high school, avoiding all athletic activities except for occasional swimming. He did not complain of dyspnea except on marked exertion.

One year before admission his physician noted irregular heart action and prescribed digitalis which the patient took regularly until admission to this hospital. Four months before admission he had a "wisdom tooth" extracted, receiving no medication before or after the procedure. Six weeks later he noted the onset of dyspnea on moderate exertion and sleeplessness. Shortly thereafter attacks of sudden breathlessness occurred which would awaken him at night. These symptoms progressed until he was forced to quit work a few days before admission because of dyspnea on minimal activity, marked weakness and inability to sleep except in the sitting position. He was referred to this hospital for evaluation.

His mother and two siblings were in good health, although the mother allegedly had had "rheumatic fever" in childhood. The father and his three sisters all had "goiters." The patient's personal and social histories were non-contributory.

Physical examination at the time of admission revealed a temperature of 37.5°C., pulse 72 with irregular rhythm, respirations 24 and blood pressure 158/60. The patient was a thin, chronically ill white man in no acute distress at rest. The skin was warm and moist with no petechiae. Marked palmar erythema was noted. No "splinter" hemorrhages were seen. There was no significant lymphadenopathy. The optic fundi were normal and a definite lid lag was present. Several definite petechiae were seen on the hard palate. The thyroid gland was not enlarged. Except for a slight precordial bulge the configuration of the chest was normal. Examination of the lungs was not remarkable. Inspection of the precordium revealed a diffuse point of maximum impulse in the sixth intercostal space at the anterior axillary line. A thrill was palpable in diastole over this area. The area of cardiac dullness was greatly increased, extending from the left anterior axillary line to 3 cm. to the right of the sternum. A grade IV high pitched decrescendo diastolic murmur was heard along the left sternal border. Over the aortic area a grade II harsh systolic murmur was present, radiating toward the neck vessels. A grade IV harsh systolic murmur was heard over the cardiac apex. A sharply localized grade III

rumbling murmur heard throughout diastole was present at the point of maximum impulse. The cardiac rhythm was totally irregular without pulse deficit. The patient's head nodded perceptibly with cardiac systole, a capillary pulse was present and "pistol-shot" sounds were heard over the femoral arteries. Liver dullness was encountered 2 cm. below the right costal margin. The spleen was easily palpable 4 cm. below the left costal margin. No pretibial edema was present. Neurologic examination was within normal limits.

The laboratory data were as follows: red blood cell count, 5,630,000; hemoglobin, 13 gm. per cent; white blood cells, 4,750; differential: basophils, 2 per cent; stab forms, 2 per cent; segmented forms, 65 per cent; lymphocytes, 25 per cent; monocytes, 6 per cent. Platelets appeared adequate in number. Urinalysis: specific gravity, 1.020; reaction, 6.5; protein, 3 plus; sugar, negative; microscopic, 10 to 20 red blood cells per high-power field. Blood cardiolipin: negative. Blood chemistry: nonprotein nitrogen, 23 mg. per cent; total proteins, 5.9 gm. per cent; albumin, 3.9 gm. per cent; globulin, 2.0 gm. per cent; protein-bound iodine, 4.9 μg. per cent; cephalin cholesterol flocculation, negative; thymol turbidity, 0.9 units. Roentgenogram of the chest: marked cardiac enlargement with left auricular and left ventricular enlargement; rheumatic heart disease with mitral stenosis and aortic insufficiency. Electrocardiogram: slow auricular fibrillation, left ventricular enlargement and digitalis effect. Culture of the throat: heavy growth of neisseria; few beta-hemolytic streptococci. Antistreptolysin "O" titer: 100 units. C-reactive protein: 1 plus. Sedimentation rate: 7 mm. per hour, corrected.

Shortly after admission seven blood cultures were drawn. Over the next three weeks these cultures revealed no growth and were discarded. On the second hospital day the patient was given antibiotic therapy with aqueous penicillin 10 million units per day, and streptomycin 0.5 gm. every six hours. Throughout the hospital course the patient was maintained on a 2 gm. salt diet and digitalis leaf 0.1 gm. per day, by mouth. On the third hospital day temperature rose to 38.5°c., and fluctuated between 38° and 39°c. for the next five days. During the first ten days in the hospital the patient remained comfortable, complaining only of pain at the site of the needle injections. During this period eight microscopic examinations of the urine revealed between 10 and 50 red blood cells per high-power field; the sedimentation rate rose slightly to 18 mm./hour, corrected. After the seventh hospital day temperature did not rise above 38.5°c., but reached a level of 38°c. daily.

On the twelfth hospital day generalized urticarial wheals developed which were attributed to the penicillin therapy. Penicillin treatment was discontinued for about twenty-four hours, and urticaria disappeared during pyribenzamine® therapy. The previous penicillin regimen was resumed the following day and the patient had no further reaction. About this time many more petechiae were noted on the hard and soft palate, although none were seen elsewhere. The patient continued to be free of respiratory distress. The spleen continued to be easily palpable.

During the fourth week of hospitalization the antistreptolysin "O" titer was 100 units; the C-reactive protein test was negative and the white blood cell count was 14,900 per cu. mm. Low grade fever and moderate tachycardia continued but the patient remained free of any distress.

Six days before his death penicillin therapy was discontinued. The following day four blood cultures and one bone marrow culture were obtained. These cultures had revealed no growth at the time of the patient's death. Four days before his death the patient's temperature fell to levels below 37.6°c. and remained below this level. On the thirty-first hospital day the patient was found lying across the bed gasping for breath with a thready, rapid pulse. Blood pressure was not obtainable and cardiac action ceased within a few minutes on July 27, 1954.

Dr. Edward Reinhard: The patient we are considering was a twenty-seven year old white salesman who was admitted to Barnes Hospital on June 23rd with the chief complaint of dyspnea. He had been in good health until the age of nine years when a febrile illness developed characterized chiefly by painful, swollen knee joints and two episodes of epistaxis. This illness was diagnosed as acute rheumatic fever and rheumatic heart disease. Three months prior to admission the patient had a "wisdom tooth" extracted, receiving no medication before or after the procedure. Six weeks later he noted onset of dyspnea characterized by sleeplessness, shortness of breath and attacks of nocturnal breathlessness. On physical examination his temperature was slightly elevated, pulse was

normal in rate but with an irregular rhythm, respiratory rate was increased and he had slight systolic hypertension with increased pulse pressure. There was a grade IV harsh systolic mitral murmur and a diastolic mitral murmur which was sharply localized to the point of maximum impulse, of grade III intensity, and rumbling throughout diastole. Dr. Massie, we may assume that this patient had rheumatic heart disease. Would you specify the valvular lesions?

DR. EDWARD MASSIE: With respect first to the aortic valve, a loud systolic murmur at the aortic area and a diastolic murmur at that area and along the left sternal border would be accounted for by aortic stenosis and aortic insufficiency. Concerning the mitral valve, an apical systolic and a diastolic rumbling murmur would indicate that the patient had mitral stenosis and mitral insufficiency. Of course if we did not suspect rheumatic heart disease so strongly, one might consider the diastolic murmur at the apex an Austin Flint murmur. I am sure, however, that the patient had aortic stenosis, aortic insufficiency, mitral stenosis, mitral insufficiency and auricular fibrillation.

DR. REINHARD: The house staff did not diagnose aortic stenosis. That is a question of interpretation of the significance and intensity of this murmur and is hard to determine from reading a chart. It is easier to tell when you have heard the murmur. Is that not correct?

DR. MASSIE: That is right. Of course, if one had a systolic thrill at the aortic area with a loud murmur as described here one would have incontrovertible evidence of aortic stenosis. I believe, however, that with a rheumatic history, a systolic murmur at the base and an associated aortic insufficiency there should be some concomitant aortic stenosis.

DR. REINHARD: It was stated in the protocol that the rhythm was grossly irregular, from which we conclude that the patient had auricular fibrillation. The first five electrocardiograms are worthy of comment. Dr. Paine has seen the entire set of records.

DR. ROBERT PAINE: These tracings bear out the diagnosis of auricular fibrillation. The changes as reported in the protocol indicate there was left ventricular strain and probable digitalis effect. The electrocardiogram did not show anything that would verify the presence of right ventricular enlargement, but certainly the record did not exclude right ventricular enlargement.

DR. REINHARD: Let us proceed to the noncardiac findings. It was stated that the patient had marked palmar erythema. There were petechiae on the hard palate which appeared in larger numbers later on during the patient's hospital course. A definite lid lag was reported, liver dullness was noted 2 cm. below the right costal margin and the spleen was definitely felt 4 cm. below the left costal margin; temperature ranged from 37° to 39°C. and the pulse was in proportion to the fever. The laboratory findings, as you will recall, showed a white cell count of 4,750 on admission, and a little later on leukocytosis to 13,900 was noted. The differential was unremarkable. There was an albuminuria of 3 plus on admission and hematuria on twelve separate urinalyses. Two urinalyses did not show red cells. The total plasma protein was 5.9, of which 2.0 gm. per cent was globulin and 3.9 albumin. The protein-bound iodine was 4.9 and the sedimentation rate rose from 17 mm. per hour on admission to 18 mm. per hour corrected. The antistreptolysin "O" titer was 100 units on admission and had not changed four weeks later. The C-reactive protein on admission was 1 plus; four weeks later it was negative. Dr. Elliott, would you discuss the x-rays?

DR. GLADDEN V. ELLIOTT: This patient had two examinations of the chest, one on the day after entry to the hospital, another one week prior to his death. Both examinations disclosed massive cardiac enlargement, with a tremendous left ventricle and huge left auricle producing a double density along the posterior margin. The lateral view substantiated this by showing displacement of the esophagus posteriorly by the left auricle. The lung fields on both examinations were essentially clear with calcified primary complex on the left and calcified hilar nodes. The vessels were not at all prominent.

DR. REINHARD: Dr. Zimmerman, I understand that you made a study last year of the incidence of an elevated basal metabolic rate in valvular heart disease. Would you discuss the significance of this patient's lid lag? The protein-bound iodine was a little low, if anything.

DR. HERBERT ZIMMERMAN: It has been known for a long time that there are diseases associated with hypermetabolism which are not thought to be due to thyrotoxicosis. In 1947 Drs. Levine and Smith reported[1] four cases of aortic stenosis

[1] SMITH, J. A. and LEVINE, S. A. Aortic stenosis with elevated basal metabolic rate simulating hyperthyroidism. *Arch. Int. Med.*, 80: 265, 1947.

in which there were hypermetabolism, complaints of nervousness, weight loss and, in one patient, a definite lid lag and proptosis. These patients all came to postmortem examination with normal thyroids. Also, it might be added that they were all treated with Lugol's solution, with no response. Last year I reviewed the records of all patients in this hospital during the past five years having a diagnosis of aortic stenosis. There were over seventy cases, among which five patients had unexplained elevated basal metabolic rates. I do not know whether one can say with certainty that these patients did not have hyperthyroidism, but the evidence seems to indicate that this syndrome can be found in patients with aortic stenosis.

DR. WILLIAM DAUGHADAY: Lid lag is a physical sign which is very difficult to evaluate, particularly on the initial physical examination, because lid lag even in thyrotoxicosis is due to increased sympathetic tone. This is mimicked by anxiety to a great extent. Frequently lid lag is noted on our first examination of a patient who does not have thyrotoxicosis; then when we return at a later time we find that the lid lag has disappeared.

DR. REINHARD: It may not, then, have any specific significance other than as a manifestation of anxiety. We can all agree, at least, that there is nothing else to suggest that this patient had any thyroid disturbance. Dr. Rouse, we all seem to think that this patient had classic rheumatic heart disease. He had a febrile illness, petechiae, splenomegaly and hematuria. Certainly a bacterial endocarditis would have to be seriously considered. Do you believe that this patient had some type of bacterial endocarditis?

DR. ERNEST T. ROUSE: Those points you mention are in favor of it, Dr. Reinhard. The patient had one very striking negative finding, though, his blood cultures. I personally believe he did not have endocarditis.

DR. REINHARD: What was the cause of his terminal illness?

DR. ROUSE: He may well have had acute rheumatic fever, although there are many factors against that diagnosis also. The hematuria and petechiae can be features of rheumatic fever, due to the arteritis which can accompany that disease. Specifically against the diagnosis of active rheumatic fever are the serologic findings, the C-reactive protein concentrations and the antistreptolysin titers.

DR. REINHARD: Dr. Glaser, would you discuss those findings and also tell us whether you think this patient had bacterial endocarditis or acute rheumatic fever, or neither?

DR. ROBERT J. GLASER: As far as the serologic findings are concerned, I agree with Dr. Rouse that the failure of the antistreptolysin "O" titer to rise to some extent, and, more importantly, the failure of the C-reactive protein to be abnormal are both against the diagnosis of acute rheumatic fever. The latter test in particular is of value as a method of following patients. It is not a specific test of rheumatic fever but in over 90 per cent of rheumatic patients followed up for a period of time the C-reactive protein test will be positive; that really is its most valuable usage. It is not infallible, but its absence here would tend to make me reluctant to make the diagnosis of rheumatic fever. Clinically there are good reasons to assume that this man may have had acute rheumatic fever. It is said that many patients with advanced rheumatic heart disease, when they go into failure or into their terminal illness, do have a reactivation of the process.

DR. REINHARD: Even if we agree that this patient might have had a reactivation of acute rheumatic fever terminally, do you think this would have accounted for his entire terminal course?

DR. GLASER: No. It should be mentioned that acute rheumatic fever is said to develop not infrequently in patients who have subacute bacterial endocarditis. If one belongs to the orthodox streptococcal school, the streptococci that cause subacute bacterial endocarditis are not usually the ones that have to do with rheumatic fever. This patient may well have had subacute bacterial endocarditis, but I agree with Dr. Rouse that the negative blood cultures, particularly with the technic Dr. Harford has set up in our clinical laboratory, are against it.

DR. REINHARD: Two primary diagnoses have been suggested, namely, subacute bacterial endocarditis and acute rheumatic fever. Dr. Smith, do you prefer either of these two, or something else?

DR. JOHN R. SMITH: This patient displayed sufficient evidence of subacute bacterial endocarditis to justify the treatment. However, I think he died of myocardial insufficiency. I have seen patients with chronic rheumatic heart disease (with mitral stenosis) who exhibited this clinical picture in their terminal illnesses: that is, rapid deterioration of cardiac function and death within days or weeks. The

heart may be greatly enlarged. Dyspnea, sweating about the face and pallor may be striking, although systemic venous pressure may not be elevated and peripheral and pulmonary edema are minimal or absent. Fever often occurs but may disappear hours or days before death. The marked enlargement of the heart and collapsing peripheral circulation even suggest severe active carditis, although acute rheumatic lesions may not be found in the cardiac tissues at autopsy. The mechanism of death, therefore, is obscure, although the events indicate the occurrence of myocardial failure with concomitant peripheral vascular collapse.

DR. GLASER: I would like to make one other point. I think that if this man had bacterial endocarditis the pathologist may well find that the process was healed. It is well known, particularly in those patients with advanced heart disease, that many of the patients who are cured of endocarditis succumb subsequently to congestive heart failure.

DR. REINHARD: Dr. Massie, I was not quite as impressed as Dr. Smith was that the evidence summarized in the protocol signified that he had any massive and overwhelming congestive failure. Still, he may have had failure. Do you think this was the cause of his death?

DR. MASSIE: On admission the findings in the lungs were not remarkable; there was no pretibial edema and certainly, from the description we have, heart failure was not prominent. Nevertheless, it probably was present. In his final days this patient might have had a fair number of pulmonary complications, but they probably were primarily pulmonary emboli; heart failure with pulmonary emboli would account for a good part of this patient's terminal illness, including fever, without forcing us to consider rheumatic fever and endocarditis. However, I believe he had one of the latter two.

DR. REINHARD: Dr. Kingsland, does the fact that this patient had a tooth extracted six weeks before the onset of his terminal illness mean anything?

DR. ROBERT C. KINGSLAND: That was a fairly long interval, Dr. Reinhard. I do not believe you could tell when the onset of symptoms of subacute bacterial endocarditis really occurred but, in my opinion, that was his underlying disease.

DR. REINHARD: This is a very common event preceding the onset of subacute bacterial endocarditis, is it not?

DR. KINGSLAND: It is.

DR. REINHARD: Dr. Paine, does the auricular fibrillation have any influence on the incidence of bacterial endocarditis?

DR. PAINE: It has been said that hearts that are fibrillating are less susceptible to endocarditis. I believe this is true because fibrillation represents a final chapter in the evolution of rheumatic heart disease, when the valves are scarred and organisms find it difficult to grow on them. It seems to me that this patient's situation might be interpreted in a third way. This might well be the occurrence of multiple emboli from a fibrillating heart. The episodes at the end were mainly embolic. The reason the blood cultures were negative is that there were sterile emboli from the auricle.

DR. REINHARD: Would you get enough to produce large showers of petechiae in the skin and mucosa?

DR. PAINE: I have seen that happen and I am sure that the behavior of the case generally fits that pattern. We could list several things that are consistent: this patient was not anemic, sedimentation rate was not very high and cultures were negative.

DR. REINHARD: It is customary to classify bacterial endocarditis into two types, the acute and the subacute, depending upon the rapidity of the progression of the disease in the untreated case. In general the acute rapidly progressive form is supposed to be due to pyogenic bacteria, whereas the subacute type is associated with organisms of lower virulence. Dr. Jones of Iowa classifies any case of bacterial endocarditis as subacute if the patient lives more than five or six weeks.[2] This patient had an illness lasting perhaps two and one half months before therapy was started, and therefore if it was endocarditis it would have had to be subacute.

I have been impressed that staphylococcic endocarditis appears to be becoming more common. It has been pointed out that petechiae and splenomegaly are common in streptococcal endocarditis and much less common in staphylococcal endocarditis, whereas arthritis, cough, chest pain, meningitis and subcutaneous abscesses are commoner in staphylococcal endocarditis. On this basis we could agree that this man did not have a staphylococcal endocarditis. If we concentrate only on those cases of bacterial endocarditis which run a subacute clinical

[2] JONES, M. Subacute bacterial endocarditis of non-streptococcic etiology. *Am. Heart J.*, 40: 106, 1950.

course, most are due to streptococci. The commonly quoted figure is that 90 to 95 per cent of subacute cases are due to some variety of alpha-hemolytic streptococci. Dr. Wood, assuming that this patient did have bacterial endocarditis, is there any information in the protocol which would lead you to doubt that this was due to some strain of the alpha-hemolytic streptococcus?

DR. W. BARRY WOOD, JR.: No. I saw the patient, as I recall, on the second or the third hospital day with the house staff and the students; at that point we had taken seven blood cultures. All agreed that this might be bacterial endocarditis and thought that treatment was indicated. There were one or two things that bothered us. The white count was low; 4,750 for bacterial endocarditis of any kind is unusual. It can occur but is not a usual count. Also, no anemia was noted and the sedimentation rate was relatively normal. Although bothered by these factors, we thought the patient should be treated. Dr. Massie has often raised the question about stopping treatment and putting the patient on salicylates. We were committed to treating this patient at the beginning and, I think, correctly. The question always arises as to how long one should maintain therapy, and I would like to ask Dr. Massie if he thinks that we treated the patient for suspected endocarditis too long. Therapy was stopped after twenty-one days.

DR. MASSIE: As a very arbitrary rule, I should advise that certainly one should treat for fourteen days.

DR. REINHARD: Dr. Wood, do you believe that the fact that this patient did not respond too well to treatment with penicillin rules out subacute bacterial endocarditis due to alpha-streptococci?

DR. WOOD: It makes me think that the patient probably did not have bacterial endocarditis, Dr. Reinhard, because most cases of subacute bacterial endocarditis due to Streptococcus viridans respond to adequate antimicrobial therapy; this patient received intensive treatment and I would have expected a good response. The patients who do not respond are those who have drug-resistant organisms, particularly in the enterococcus group. In these cases one can culture the organism from the blood, so the fact that there were no positive blood cultures plus failure to respond to penicillin leads me to agree with Dr. Paine that perhaps this condition was old rheumatic heart disease with resultant complications rather than either active rheumatic fever or endocarditis.

DR. REINHARD: In the article in the *American Heart Journal* referred to previously, Jones reviewed from the literature all the cases of subacute bacterial endocarditis in patients living more than five or six weeks, excluding all cases of streptococcal origin. There are a large number of organisms that can cause subacute bacterial endocarditis, namely, Pseudomonas aeruginosa, micrococcus, Neisseria gonorrhoeae, Neisseria meningitidis, other neisseria, brucella, hemophilus, Diplococcus pneumoniae, gram-negative rods, corynebacterium, Mycobacterium tuberculosis and actinomyces. I take it from what you said, Dr. Wood, that you believe that we do not have to consider seriously any of these.

DR. WOOD: Dr. Harford has set our procedure in the laboratory now so that in these cases thioglycolate culture is made as well as a routine broth culture. With the methods now in use we would pick up most of the organisms that Dr. Jones has listed. We would not grow the tubercle bacillus but this is a pretty uncommon cause of bacterial endocarditis; certainly we would not worry about it too much. Most of the other organisms would grow out of the media that we use, with the possible exception of the brucella organism.

DR. REINHARD: Dr. Harford, perhaps we had better go back to the blood cultures in more detail. Seven blood cultures were drawn during the patient's first twenty-four hours in the hospital before penicillin therapy was instituted. During this time the patient's temperature did not go above 37.5°C. These cultures were done routinely and by special methods. They were all negative and were discarded at the end of three weeks. On the fifth hospital day two blood cultures were obtained. At that time the patient's temperature was fluctuating between 38° and 39°C. Penicillinase was added to the cultures, which were also negative at the end of three weeks and were discarded. Five additional blood cultures, including at least one culture on a special medium for fungi, and a bone marrow culture were obtained during the last three weeks in the patient's hospital course; none of these showed any growth at the time of the patient's death. Now if this were bacterial endocarditis, what kind would you think most likely? Or do you think this was not bacterial endocarditis?

DR. CARL G. HARFORD: We cannot exclude bacterial endocarditis on the basis of negative

blood cultures; I say that not because I think that the media would not grow the organisms concerned, but because there are forms of subacute bacterial endocarditis in which the disease can be diagnosed post mortem and organisms apparently are not actually in the blood. One of the prominent reasons is that the organisms are sometimes covered over by the fibrin of the vegetation and do not get into the blood stream. It has been pointed out that the fatality rate for patients with subacute bacterial endocarditis who do not have positive blood cultures is higher than for those in whom the diagnosis can be made by this procedure. One of the reasons often given is that treatment is not instituted because a definite diagnosis cannot be made. It seems to me that it was necessary to treat this patient for subacute bacterial endocarditis because of the general clinical picture and because that disease could not be excluded on the basis of the clinical data.

DR. REINHARD: This patient was thought to be improving by the physicians taking care of him. His temperature had certainly been lower for several days when he was found lying across his bed gasping; he died shortly thereafter. Dr. Smith, what do you suppose was the cause of death?

DR. SMITH: It could be reasonably argued that massive pulmonary embolism occurred, or that a deleterious cardiac arrhythmia supervened to evoke sudden death. Heart failure may occur without peripheral vascular congestion. On the other hand, in the usual case of congestive heart failure, it would seem that the venous transport of blood from the periphery (by capillary vis-a-tergo and other propulsive forces) exceeds the capacity of the heart to accept venous blood for onward passage. Venous congestion then gradually occurs and becomes intensified by salt and water retention and resultant expansion of blood volume. However, it seems to me that in the clinical instance here myocardial failure progressed to the point where life could not be supported, but with sufficient vascular blood pooling (possibly venular) so that venous engorgement was not apparent.

DR. MASSIE: The patient had aortic stenosis in which sudden death is always a possibility; of course, the patient could have had a cerebral embolus.

DR. WOOD: Dr. Massie, would a central embolus cause a patient to die this rapidly?

DR. MASSIE: Your point is well taken. Aortic stenosis with sudden death or pulmonary embolism are the two most likely possibilities.

DR. GLASER: One other lesion, the so-called non-bacterial thrombotic endocarditis, could have produced this picture. It is postulated that some of those people have had bacterial endocarditis which is healed in the manner in which Dr. Harford suggested, and pieces of sterile vegetation break off. We have seen at least one patient in this hospital with a resistant strain of endocarditis who obtained a spontaneous cure and was a candidate for that sequence. She has rheumatic heart disease and she obviously has vegetations which are no longer infected. That is one other possibility.

DR. REINHARD: One would state that this patient might have had thrombotic endocarditis, but it would be perhaps unlikely that that would be the explanation of the whole terminal illness. Would you agree?

DR. GLASER: Yes.

DR. HARFORD: This patient did not have anemia. Could that be explained by a relatively short period of time having elapsed since the onset of a possible subacute bacterial endocarditis?

DR. REINHARD: Yes, certainly the anemia due to chronic infection does require a certain length of time to develop, depending upon the severity of the infection. A low-grade infection such as one has on the heart valve might persist for a good many months before any significant anemia would develop. That is quite possible.

DR. HARFORD: How long had the patient had symptoms?

DR. REINHARD: It is difficult to say just when the terminal illness began, but he had had symptoms for two and a half months. They were strikingly different from those symptoms he exhibited prior to that time. The house staff diagnosed the condition as rheumatic heart disease with mitral and aortic involvement, chronic auricular fibrillation, subacute bacterial endocarditis and rheumatic heart disease suspected. I think it is impossible to make a definite diagnosis here but I prefer a diagnosis of some form of subacute bacterial endocarditis. The patient might well have had multiple emboli and I believe did have multiple emboli associated with the final hours of his life.

PATHOLOGIC DISCUSSION

DR. DANIEL L. ROSENSTEIN: The most significant gross pathologic lesions were in the heart,

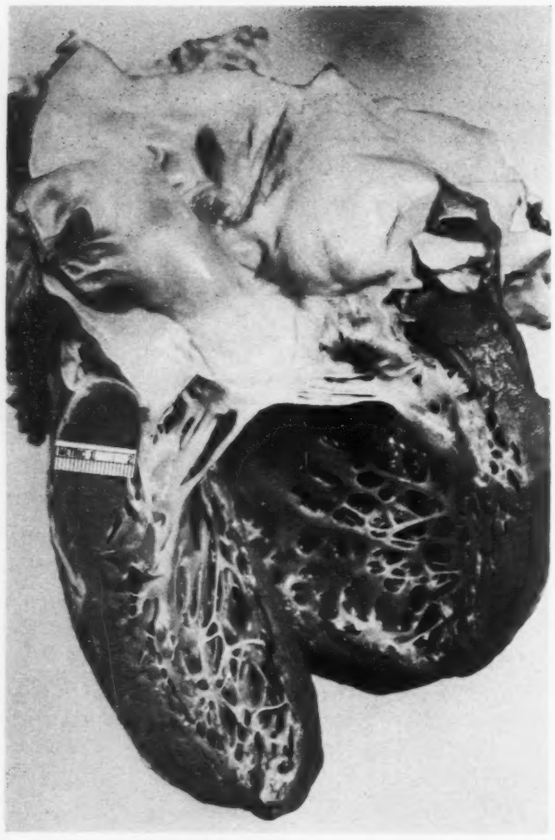


FIG. 1. The heart with left atrium and ventricle opened through mitral valve to show greatly thickened myocardium and scarring and stenosis of valve.

kidneys, spleen and lungs. The heart weighed 840 gm. and was greatly enlarged. Figure 1 is a photograph of the opened left ventricle and atrium. The atrium was dilated and thick walled and there was a patch of thickened, rough endocardium above the posterior leaflet of the mitral valve. The thickness of the myocardium of the left ventricle was 16 mm. and that of the right was 6 mm. Small scattered foci of fibrosis were grossly discernible in the posterior wall of the left ventricle. The aortic valve had thickened cusps, the edges of which were contracted and rolled toward the sinuses. There were adhesions between the cusps at the commissures, and between two of the cusps there was a lobulated calcified mass 5 mm. in diameter. The position of the cusps of this valve were such that it was undoubtedly insufficient. The mitral valve leaflets and chordae tendinae were greatly thickened and the valve moderately stenotic. The commissures were blunted by fibrous adhesions and in each leaflet there was a small calcified mass.

The kidneys were moderately congested and in the lower pole of the left kidney there was a deep sharp scar of the type that follows healing of an infarct. The spleen was enlarged to a weight of 345 gm. and was congested. The parenchyma contained prominent follicles. There was also moderate congestion of the liver and the mucosa of the upper gastrointestinal tract. The lungs were somewhat firmer than usual. Their color was tan and on incision there was minimal evidence of edema.

In summary the most significant findings were chronic passive congestion of the lungs and cardiomegaly which was predominantly left-sided with the anatomic findings of aortic insufficiency and mitral stenosis with some calcification.

DR. W. STANLEY HARTROFT: The central findings in this case are those of old scars in the endocardium, myocardium and valves of the heart with no evidence of active lesions. The myocardial scars are quite typical of those found in cases of old rheumatic myocarditis. Figure 2 illustrates such an area with fragmented ends of atrophic myocardial fibers buried in a rather loose fibrous stroma. These isolated fragments of muscle were once thought to be the source of the Aschoff cells in rheumatic nodules but are more typical of the late stages of the lesion and are now interpreted as an effect of the inflammation and scarring rather than a specific part of the inflammatory response. Figure 3 shows one of the typical, smaller and rather fusiform scars about blood vessels of the interstitial septa. This slide was stained by the periodic acid-Schiff method and the rather amorphous dark mass in the center of the illustration stained positively in the manner of the so-called mucopolysaccharides rather than like the non-specific reaction of ordinary fibrous tissue in a scar. These remnants have been said to represent the tombstones of Aschoff nodules. If so, they are the only evidence that is even suggestively specific of the rheumatic process in this patient.

Microscopic sections of the lungs show dilated alveolar spaces that are held rigidly open by turgid capillaries. This might be called pseudo-emphysema, but it is not true emphysema as the walls of the alveoli are intact. The advanced congestion of all the small pulmonary vessels and the capillaries is well shown in Figure 4 in which the erythrocytes are stained darkly. Despite the congestion there is very little

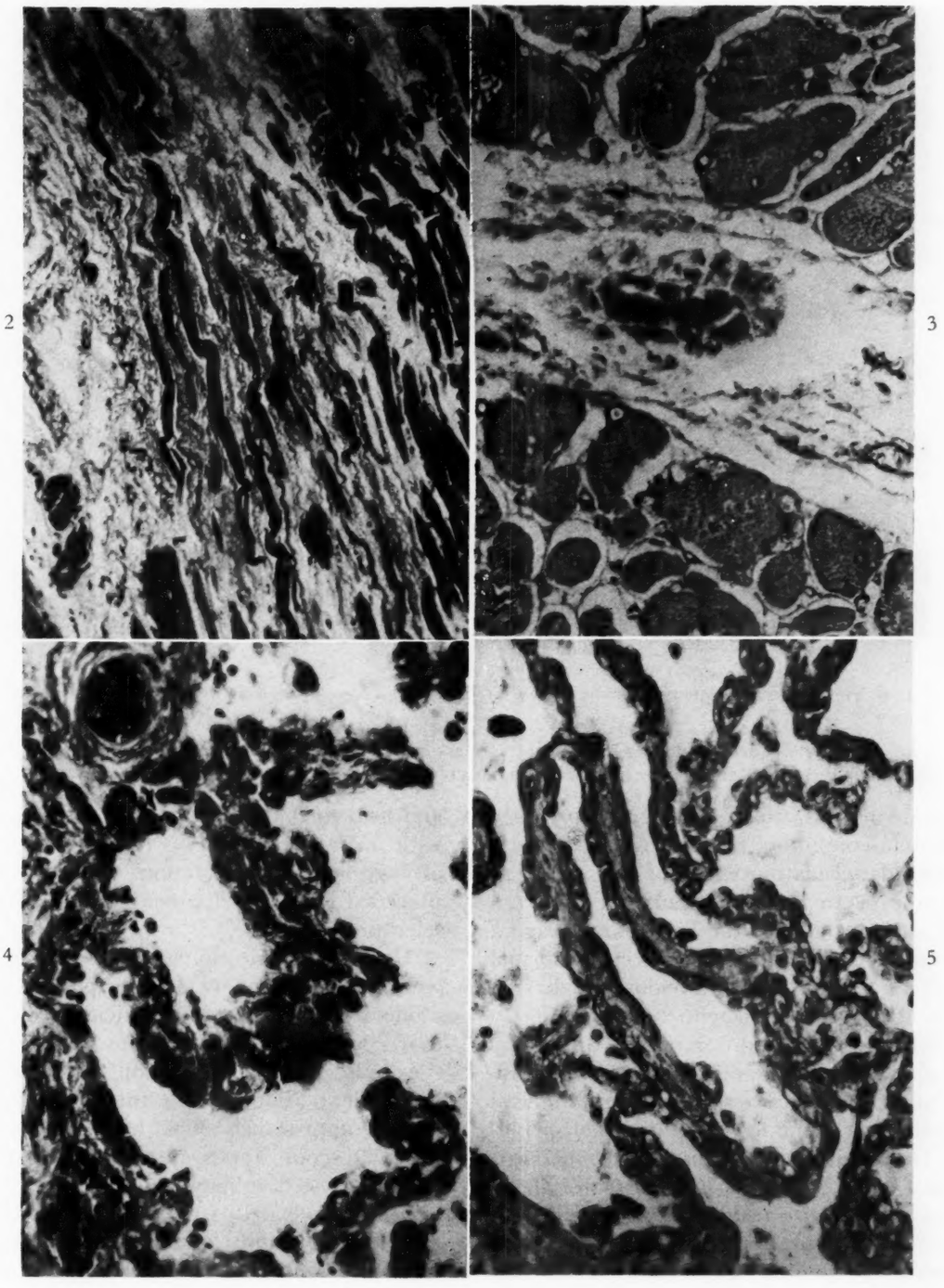
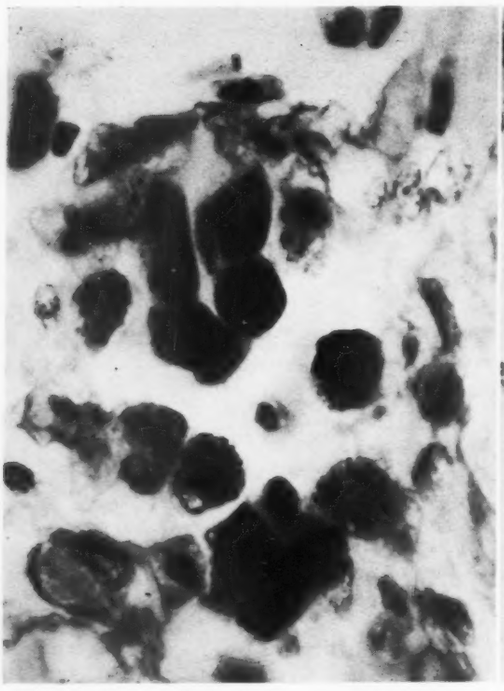


Fig. 2. Focus of fibrosis in myocardium with atrophy and fragmentation of muscle fibers. This appearance is often seen in chronic heart disease following rheumatic fever.

Fig. 3. Fusiform interstitial and perivascular nodule in the heart. Location and shape of these scars is reminiscent of Aschoff nodules and the amorphous material in the center stains with periodic acid-Schiff stain in the manner of fibrinoid.

Fig. 4. Advanced congestion of capillaries and small arteries in the lung. Turgid capillaries hold open the alveoli.

Fig. 5. Alveolus with greatly thickened basement membrane in alveolar wall.



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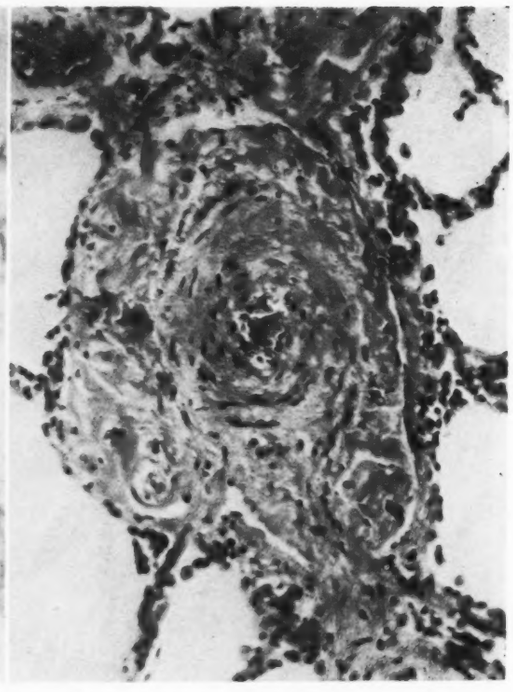

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FIG. 6. Hemosiderin-laden phagocytic cells that lie within alveolar walls as well as being free in the lumen.

FIG. 7. Advanced arteriosclerosis of small pulmonary artery that has progressed almost to point of occlusion and is thought to have originated on basis of organization of small emboli or mural thrombi.

precipitate in the alveoli to indicate the presence of a protein-containing edematous fluid. Figure 5 shows advanced thickening of the basement membrane of an alveolar septum. This is not generalized throughout the lung but is present here and there. All this material is very abnormal and where present would obviously make the interchange of gases inefficient.

In this lung, in addition, there are many macrophages which are filled with hemosiderin. A few of these can be seen peeling from the wall of the alveolus in the lower right corner of Figure 5. The origin of these cells has been debated for many years, but in this lung there are places such as that shown in Figure 6 where the cells appear actually to lie in the alveolar septal membrane suggesting that they have their origin there.

A final prominent lesion in these lungs is a widespread advanced arteriosclerosis and arteriolosclerosis. This is shown in the vessel in Figure 7 where the lumen is ridiculously small for the size of the vessel. Such vessels are almost typical of chronic mitral stenosis. Recent studies have strongly suggested that these lesions arise by organization of small emboli and mural thrombi and lead to the pulmonary hypertension found with mitral stenosis. This represents a reversal of the older interpretation that hypertension preceded the development of the vascular sclerotic lesions.

The microscopic changes in the other viscera were not very striking. In the spleen there was moderate congestion and follicular hyperplasia that could have been perhaps associated with the mild penicillin reaction experienced by the patient. The scar in the kidney had the typical appearance of a healed infarct, but the microscopic appearance of the arteries at its apex suggested it may have resulted from an arteritis associated with the rheumatic fever rather than simply an embolus. In the liver there was a suggestion of atrophy of the centrilobular cells secondary to the mild congestion present in nearly all the organs.

In summary, the pathologic changes were those of a definite chronic endocarditis with mitral stenosis, aortic insufficiency and myocardial scarring accompanied by definite but not advanced evidence of congestion in most of the viscera. These are exactly the findings that occur in the type of case to which Dr. Smith

referred. There is little evidence of the changes of advanced congestion and edema of the lungs and other viscera seen in acute myocardial failure as it is generally recognized. The changes that are present seem perfectly compatible with the physiologic explanations offered by Dr. Smith.

Final Anatomic Diagnoses: Chronic endocarditis with mitral stenosis and aortic insufficiency; hypertrophy and dilatation of the heart with myocardial scarring; chronic passive congestion of the lungs; moderate congestion of the liver, spleen, kidneys and mucosa of the gastrointestinal tract.

Acknowledgment: Illustrations were made by the Department of Illustrations, Washington University School of Medicine.

Research Society Abstracts

Association for the Study of Liver Diseases

ABSTRACTS OF PAPERS PRESENTED AT THE FIFTH ANNUAL MEETING, CHICAGO, ILLINOIS, OCTOBER 28, 1954

SYMPOSIUM ON JAUNDICE (MODERATOR, LEON SCHIFF, CINCINNATI, OHIO)

METABOLISM OF BILE PIGMENTS. *Irving M. London.* New York, N. Y.

Hemoglobin, myoglobin and the respiratory heme enzymes occupy a central role in metabolic processes for they are concerned with the processes by which oxygen is made available to the animal cell and with the processes of cellular oxidation. In the biologic synthesis of heme, glycine and succinate are utilized for the formation of delta-amino-levulinic acid from which a monopyrrole, probably identical with porphobilinogen, is formed. This monopyrrole can be converted to uroporphyrin, coproporphyrin and protoporphyrin.

The conversion of hemoglobin to bile pigment may proceed via the formation of choleglobin. Evidence is presented to indicate that this conversion might also proceed via hematin. In the intestine bilirubin undergoes a series of reductions to mesobilirubinogen and stercobilinogen which on oxidation yield urobilin and stercobilin, respectively. In the presence of infection, or after the administration of certain antibiotics orally, a dextrorotatory urobilirubinogen is formed which on oxidation yields dextrorotatory urobilin.

Recent studies on the direct and indirect van den Bergh reactions indicate qualitative differences in the chemical constitution of the pigments which give these reactions.

Studies on the origin of bile pigment indicate that in normal man at least 10 to 15 per cent of total bile pigment is derived from one or more sources other than the hemoglobin of mature circulating erythrocytes. In disease states such as pernicious anemia and congenital porphyria the proportion derived from alternative sources may be increased. Investigation of the nature of these alternative sources has revealed that hematin can be converted to bile pigment in the mammalian organism. Studies are now in progress on the possible conversion of other naturally occurring porphyrin compounds to bile pigment.

INTERRELATIONSHIPS AMONG HEPATIC TESTS. *Leslie Zieve.* Minneapolis, Minn.

From a study of interrelationships among liver function tests one may expect to (a) bring out relationships not apparent on the surface, (b) discover the tests having independent significance, and (c) find a rational basis for discarding tests. Such an analysis as applied to patients with acute viral hepatitis revealed that each of nine quantitative tests representative of the gamut of hepatic tests was effective in differentiating the patient with hepatitis from the normal. All nine taken together in optimal combination were no better than four of the tests taken in combination. The observed effectiveness of the five tests (galactose tolerance, thymol turbidity, per cent cholesterol esters, serum bilirubin and urine urobilinogen) not having independent significance was accountable in terms of the four having independent significance and comprising the minimal combination. These four tests were (1) bromsulfalein retention, (2) zinc sulfate turbidity, (3) hippuric acid excretion, and (4) coproporphyrin excretion. The largest contribution to the observed effectiveness of the five tests without independent significance was made by factors underlying the coproporphyrin test.

In a similar group of patients with cirrhosis, the same four tests were found to have independent significance. Unlike the hepatitis cases the largest contribution to the observed effectiveness of the five tests without independent significance was made by factors underlying the bromsulfalein test.

A simple analysis of the relationship of various tests to the degree of bilirubinemia in patients with cirrhosis, viral hepatitis and obstructive

jaundice resulted in the following observations: Percentage cholesterol esters was largely dependent on the degree of jaundice in each of the three groups. A moderate correlation between bromsulfalein retention and bilirubinemia was observed in each of the three disease groups. An inverse relationship, similar in magnitude, was noted for the hippuric acid test in the cirrhosis and hepatitis patients. With two exceptions, no appreciable correlation with the degree of jaundice was noted for the galactose tolerance, urinary coproporphyrin, urinary urobilinogen, cholesterol, thymol turbidity, zinc turbidity, cephalin flocculation and alkaline phosphatase tests. The galactose tolerance and urinary coproporphyrin tests each correlated moderately well with the degree of jaundice in the hepatitis patients only. Though the alkaline phosphatase is usually increased in the presence of obstructive jaundice, no relationship was observed between the degree of abnormality and the degree of jaundice.

HEPATITIS WITH MANIFESTATIONS SIMULATING BILE DUCT OBSTRUCTION ("CHOLANGIOLITIC" HEPATITIS). *Edward A. Gall.* Cincinnati, Ohio.

This study is concerned with the lesions observed in liver biopsy specimens from fourteen patients in whom the initial clinical course incorrectly indicated major biliary duct obstruction. This information and that gathered from clinical and laboratory observations were compared with similar data derived from thirty-five patients with classical viral hepatitis. The patients with obstructive manifestations proved to be in the older age range with more prolonged jaundice. Other clinical features were similar in both groups although those simulating obstruction more often exhibited pruritus, acholic stools, elevation of blood lipids and serum alkaline phosphatase, and negative results with the flocculation tests.

The histologic pattern varied somewhat but there was an obvious relationship between the two, and the lesion contrasted strikingly with those found in the presence of true bile duct obstruction. The prolonged ("cholangiolitic") form of hepatitis was highlighted by inflammatory predilection to periductal regions, perilobular pseudoductular epithelial budding and bile stasis. These were all present to a variable and lesser degree in the lesions of viral hepatitis as ordinarily encountered. There was no consistent correlation between individual morphologic alterations and the various features of the clinical syndrome. The problem of clinical distinction between hepatitis simulating obstruction and surgical obstructive jaundice should be resolved in most instances by recourse to needle biopsy of the liver.

SURGICAL ASPECTS OF (OBSTRUCTIVE) JAUNDICE. *Julian A. Sterling.* Philadelphia, Penna.

The surgeon's approach to obstructive jaundice is influenced by the need to assure normal bile flow as a method for restoring normal hepatic function. At operation, supplementary assistance to gross inspection and palpation should be available. These include manometric methods, radiologic technics, rapid examination of removed tissues and facility for duodenotomy.

The patient's condition usually determines whether the surgeon can remove and reconstruct or merely palliate and drain. Whether bile is permitted to reach the duodenum is not as important as the relief of obstruction. Secondary surgery to reconstruct a proper route for bile flow into the intestines may be done at a later date after hepatic function has been restored.

Discussion of the Preceding Presentations and General Remarks

CECIL J. WATSON (Minneapolis, Minn.): Dr. London has given us an excellent survey of many of the aspects of the bile pigment problem. The important studies of the significance of glycine in the biosynthesis of heme and the observation that some of the stercobilin in the feces is not derived from mature circulating erythrocytes are of great interest. It was not surprising to find that this was true in pernicious anemia, as previous data had strongly indicated that much of the urobilinogen of the feces in this disease in relapse was not derived from any ordinary blood destructive process, and Whipple, in his pigment-pool concept, in addition to Minot and Jedlicka, had favored this concept. In our own studies it was repeatedly observed that the amount of urobilinogen excreted in the feces was far out of proportion to the decline of circulating hemoglobin over a given period of time, taking into account the fact that in pernicious anemia, unlike the ordinary hemolytic anemias, the rate of replacement was very slow. It was much more surprising to learn from the N^{15} glycine studies of London and his co-workers that under normal conditions about 15 per cent of the fecal stercobilin is derived from other than the hemoglobin of mature circulating erythrocytes. Here it seems that there are two main possibilities. (1) This fraction does represent pigment partially built up on the way to heme but is excreted without being used, somewhat in the sense

of the Whipple pigment-pool concept. (2) An excessive number of red blood cells are formed and at once destroyed. This would be in line with the general lavishness of compensation in excess which characterizes so many natural phenomena. Further study must decide between these possibilities.

We have recognized since our early work on crystalline stercobilin that fecal urobilinogen is not the sole bile pigment derivative excreted in the feces. At the time that stercobilin was crystallized it was regularly noted that it was accompanied in approximately equal amounts by a dark brown, almost black, substance to which the name "copronigrin" was given. This substance was characterized by an insoluble zinc complex, in contradistinction to the readily soluble green fluorescing zinc complex of stercobilin and urobilin. Siedel later showed that mesobilifuscin, a dipyrrylmethene derived from bilirubin, has these characteristics, and the isolation of mesobilifuscin from the feces by Siedel leaves little doubt that it is essentially the same as the substance earlier designated as "copronigrin." Thus it appears that some of the bile pigment from destroyed hemoglobin or possibly from other sources as mentioned in the foregoing, is represented not as a tetrapyrrylmethene of the urobilinogen type, but as a dipyrrylmethene, a molecule half as large. Much further study is necessary and is now in progress to determine the significance of mesobilifuscin and whether or not its excretion in the feces varies in a manner differing from that of urobilinogen excretion. It is conceivable that this might have considerable significance in certain states such as hepatic disease and rheumatoid disease in both of which it has recently been claimed that a shortened red cell life span may not be associated with a heightened urobilinogen excretion.

A word about the problem of the serum bilirubin. Whatever the exact basis of the prompt, direct versus the delayed or indirect van den Bergh reaction shall ultimately prove to be, it has become increasingly clear that these fractions have genuine validity in the study of disease. One of the great difficulties in determining the basis of the difference in these reactions may be ascribed to chemical artefact. It is clear that chemical treatment of one type or another of bilirubin-containing sera may alter the character of the reaction. The most recent fundamental studies of the van den Bergh reaction by Najjar in this country and by Cole and Lathe in England have given widely varying results. Najjar believes that the prompt, direct reacting type is a metal complex and the indirect type a globulin complex, while Cole and Lathe state that the indirect is simply free bilirubin and the direct a substance chemically distinct from bilirubin. They state further that bile contains relatively little bilirubin, this term being reserved for the indirect reacting type. This, however, we find very difficult to understand as Fischer showed many years ago that crystalline bilirubin from cattle gallstones is identical with the crystalline bilirubin isolated from old hemorrhages. Porsche devised an excellent method for isolating bilirubin of the same type from pig bile. Lowry and I have recently shown that crystalline bilirubin can be isolated from human feces in good yield shortly following administration of aureomycin. In addition, Snapper showed years ago that the crystals of bilirubin isolated from obstructive jaundice serum were the same as those from (indirect reacting) hemolytic jaundice serum. All of these observations indicate that the bile does contain relatively large amounts of bilirubin and, as mentioned, it has been shown to be identical with bilirubin appearing in extravasations of blood, in other words the "hematoidin" of Virchow. These comments are not meant to imply that the studies of Cole and Lathe are incorrect or without significance but it is important to question to what extent their results have been influenced by chemical manipulations, and further work is necessary in this regard. The possibility must be considered that a differing physical state of bilirubin in direct reacting sera, rather than a structural difference, influences its behavior in the chromatographic method used by Cole and Lathe.

Dr. Zieve's observations on the fundamental interdependence of certain liver functions and the emergence of certain factors common to a group of functions is believed to be of much significance. It might be pointed out that the lack of interdependence of the urinary coproporphyrin and the bromsulphalein factors in the cirrhosis group and its presence in the hepatitis group may possibly be explained by the fact that in the latter the excessive urinary porphyrin excreted in the urine is the type I isomer. There is considerable evidence that this excess is related simply to regurgitation of bile or simple hepatocellular excretory functional impairment; hence, in this instance interdependence would be expected. In the cirrhosis group, if mainly in alcoholics, as in Dr. Zieve's study, the excessive urinary porphyrin is a type III isomer. This is probably related to an intrinsic metabolic impairment, although whether in the liver or bone marrow is not yet known. Here one would expect a lack of interdependence. Further study along these lines may prove of great interest.

With respect to the problem of cholangiolitic hepatitis, I understood Dr. Gall to say that a distinction could almost always be made histologically between this condition and obstructive jaundice. If this is true his criteria will be of much help to other pathologists who are having difficulty with this problem. We have had considerable trouble in interpreting liver biopsies in this respect, and on not a few occasions the initial interpretation was eventually shown to be incorrect. Partly on this ground we have come to rely more and more on cholangiography and liver biopsy, either peritoneoscopic or through a small laparotomy under local anesthesia, in those cases where other features have not served to distinguish

cholangiolitic hepatitis or cirrhosis from extra-hepatic biliary obstruction.

It may be emphasized that we have never used the term cholangiolitic in the histologic or morphologic sense but purely from the standpoint of functional cholangiolar disturbance. When Dr. Hoffbauer and I first started using this term we were impressed by the lack of hepatocellular functional impairment in the presence of outspoken evidence of regurgitation of bile but, at the same time, without any evidence of specific or well defined lesion of the main bile passages. In these instances it seemed inescapable that when the histology is relatively normal there must be a functional disturbance of the cholangiolar system permitting a return of bile to the blood, either directly or via the lymph. It was thought, too, that this might account, at least in part, for bile thrombi, in other words an inspissation of bile due to greater loss of water than solute.

It should also be emphasized that cholangiolitic hepatitis or cholangiolar impairment is often only a part of the total picture. The situation is perhaps somewhat analogous to nephrosis and the nephrotic "einschlag" of Volhard which often accompanies glomerulonephritis to some degree. Frequently in hepatitis there is cholangiolar impairment and in some of the prolonged cases it may persist for months or years as an isolated phenomenon with relatively normal function of the liver cells. In some instances the cholangiolar system appears to be the only part of the liver which has been impaired even from the outset. Such injuries as those due to arsphenamine, methyl testosterone and, more recently, thorazine appear often to be of this type. Thus use of the term cholangiolitic hepatitis or cirrhosis should imply a marked functional impairment of the cholangiolar system with regurgitation of bile but with little or no evidence of hepatocellular functional impairment.

HISTOGENESIS OF COARSE NODULAR CIRRHOSIS. *Hans F. Smetana.* Armed Forces Inst. Pathology, Washington, D. C.

There is circumstantial evidence that coarse nodular cirrhosis is one of the possible but rare sequelae of viral hepatitis, although it may also be the consequence of toxic damage to the liver by arsenic, phosphorus or mushroom poisoning. The clinical symptoms produced by this condition are often indistinguishable from those of portal cirrhosis, and the diagnosis can be suggested only on the basis of a history of viral hepatitis. Since it may take several years for portal hypertension or hepatic insufficiency to develop, the history of hepatitis may by then be rather vague.

The gross appearance of the pathologic specimen of coarse nodular cirrhosis is characterized by replacement of the hepatic parenchyma by nodules measuring one or more cm. in diameter, which produce great deformity in the shape of the liver. Microscopically, the individual nodules are made up of composite liver lobules which are separated by fibrous bands containing reticulum fibers, fibrous connective tissue and small bile ducts. The portal triads within the composite nodules are smaller than normal and their spacing as well as their relationship to efferent veins is irregular. The liver cells are fairly normal in appearance except that their radial arrangement about efferent veins is often distorted. The reticulum of the nodules appears normal.

Histologically, the appearance of the composite nodules of coarse lobular cirrhosis is so unlike that of the pseudolobules of portal cirrhosis as to suggest an entirely different histogenesis. The pseudolobules in portal cirrhosis are single lobules and they lack a properly placed efferent vein from which columns of liver cells radiate. No portal triads are seen in the pseudolobules. It appears that the damage leading to portal cirrhosis affects groups of liver cells of each individual lobule as well as the reticulum in this area. Regeneration of liver cells therefore is irregular and often concentric. Coarse lobular cirrhosis, on the other hand, represents the healing phase of near fatal necrosis of liver tissue due to the virus of hepatitis or to toxins, which leaves only a few islets of liver cells intact. From these islets regenerating nodules of liver cells grow in size until their expansion is halted by similar neighboring nodules, while the collapsed stroma of the necrotic portions furnishes the septa. The tissue making up these composite nodules resembles normal liver tissue fairly closely except for distortion of cell columns and lack of portal triads. Reorganization is gradually accomplished by ingrowth of bile ducts from the septa into the regenerated nodules of liver cells and by regrouping of vessels. Only if enough liver cells are spared during the original attack can sufficient liver tissue be regenerated. Such regenerated liver parenchyma may function reasonably well for years but eventually difficulties in circulation within the liver lead to portal hypertension and its consequences. If anoxemia ensues because of general circulatory collapse, gastrointestinal hemorrhage, coronary disease or any other cause, the nodules may become necrotic, leading usually to hepatic insufficiency.

MASSIVE HEPATIC NECROSIS IN A YOUNG MAN. *W. Stanley Hartroft and Robert E. Shank.* Washington Univ. Medical School, St. Louis, Mo.

Clinical and pathologic findings were described pertaining to a young white man (age twenty-nine) who had manifestations of heat prostration ten days before death. At autopsy, massive hepatic necrosis was discovered. The patient had been a social worker in New York City, where he had been exposed to jaundiced people and rats, and he had occasionally worked with cleaning solutions. He had no alcoholic habits. At the height of the summer heat, he hitchhiked from New York City to St. Louis, and the next day, although tired, ran a six-mile race when the recorded temperature was 86°F. and the relative humidity was 54 per cent. Following the race he collapsed with characteristic symptoms of heat stroke, except that marked hyperpyrexia and defective sweating were absent. Laboratory data revealed evidence of hepatic dysfunction, which became increasingly severe along with jaundice during his ten-day hospital stay prior to death. His temperature on admission to the hospital was 39.2°C. Subsequently it dropped and did not go above 39°C. throughout the rest of the course, except during the terminal period. At autopsy, massive hepatic necrosis was discovered and generalized icterus of all viscera. In microsections of the small wrinkled yellow liver only narrow rims of parenchyma in periportal positions had survived. A moderate degree of chronic inflammatory reaction was present in portal triads. Pseudocholangioles had formed at the edge of the surviving tissue. Hemosiderin, hemofuscin and ceroid pigments were present in the surviving parenchymal cells and in the Kupffer cells. Little stainable fat could be demonstrated except in the walls of hepatic arterioles, where it presented an unusual and striking appearance. Microscopic observations of relevant interest in other organs were confined to the demonstration of hemorrhages in the dentate nuclei of the brain during the terminal period. Although the lesions in this case might be compatible with published descriptions of hepatic necrosis due to heat stroke, the patient's history and his course in the hospital, as well as the anatomic findings, appear more compatible with a diagnosis of infective hepatitis of viral origin. The possibility was raised that massive hepatic necrosis in heat stroke may sometimes have an infective origin characterized by a fulminating course precipitated by the superimposed stress induced by hyperthermia.

JAUNDICE ASSOCIATED WITH ADMINISTRATION OF CHLORPROMAZINE. *Joseph M. Gambescia, Joseph Imbriglia, Peter Galamage and William Winkelman, Jr.* Hahnemann Medical College, Philadelphia, Penna.

Five cases were presented of persons developing an icteric state following administration of chlorpromazine. The clinical picture was characterized by an acute febrile response with malaise, anorexia, chills, myalgia, followed by dark urine, pruritus and jaundice. The biochemical pattern in all cases showed hyperbilirubinemia, choluria and hyperphosphatasemia associated with normal cephalin-cholesterol flocculation, normal thymol turbidity and flocculation, normal zinc turbidity and serum protein partition. In some cases an eosinophilia (up to 26 per cent) and hypercholesteremia was noted. Needle liver biopsy specimens revealed intrahepatic cholestasis with a lesion affecting the cholangiole characterized by eosinophilic infiltration.

Certain therapeutic approaches were discussed. The use of antihistamine and sodium dehydrocholate had no beneficial effect. ACTH and cortisone were accompanied by prompt beneficial response. No fatalities have been encountered.

The entity is of considerable importance because of (1) its resemblance to viral hepatitis with its accompanying public health implications; (2) its resemblance to extrahepatic obstruction and its surgical implications; (3) its morbidity and its economic implications.

INTRAHEPATIC OBSTRUCTIVE JAUNDICE IN INFANTS. *Ruth C. Harris.* Columbia Univ. College of Physicians and Surgeons, New York, N. Y.

During the past few years intrahepatic disease has come to be recognized as a relatively frequent cause of obstructive jaundice in infants under six months of age, occurring with even greater frequency than does congenital atresia of the bile ducts. In cases of intrahepatic biliary obstruction the syndrome usually follows and often blends with the clinical picture of jaundice of prematurity or with that of erythroblastosis fetalis and occurs as a rule in patients who have been treated either by exchange transfusion or by simple transfusion. Similar cases observed by others have been reported in the literature as examples of viral hepatitis, while additional

instances have been included in the "inspissated bile syndrome." In our own case material, a large proportion of infants so afflicted have been of Italian parentage. Clinically these infants usually reveal persistence or recrudescence of jaundice present in the neonatal period, with the appearance of light-colored stools and dark urine. They may or may not appear ill but generally show some retardation of growth and may develop rickets during the course of the disease. The liver and often the spleen are enlarged and firm. The total serum bilirubin concentration may vary from 6 to 30 mg. per 100 ml., "direct" bilirubin comprising approximately one-half of the total. Cephalin flocculation and thymol turbidity tests usually give negative results. Serum alkaline phosphatase level is elevated in approximately two-fifths of the cases. Zinc sulfate turbidity is low or normal in infants with preceding erythroblastosis or with a history of prematurity but is elevated in the other cases of this group. Liver biopsy yields sections which are surprisingly alike in all of these cases. Liver cells at or near the centers of lobules are found filled with yellow, non-iron-containing pigment which appears similar to that filling the bile canaliculi. The liver cells are swollen, and many are multinucleated. The portal areas show an increase in mononuclear cells and slight proliferation of bile ducts. When a hemolytic process has preceded the development of obstructive jaundice, islands of erythropoietic and myelopoietic tissue are scattered throughout the lobules. Sometimes a few necrotic cells are found. The same histologic picture has been found in patients with a wide variety of disease pictures, such as erythroblastosis, serum hepatitis, acquired hemolytic anemia, cytomegalic inclusion disease and prematurity.

It appears that an insult to the liver during the first six months after birth results in a characteristic response, giving a picture similar histologically to that described in adults by Lucké and attributed by him to viral hepatitis. Swollen liver cells, overdistended with bile, occlude the bile capillaries, causing the obstructive phase of the disease. The inflammatory response seems minimal but the evidence of regeneration, as seen by the giant hepatic cell response, is good. The presence of many mononuclear cells in the portal areas, the myelopoiesis and erythropoiesis found in infants with this syndrome are related to the age of the patient and the need for additional blood cell formation. The mechanism of damage to liver parenchyma is quite different from that of extrahepatic atresia where hepatic cellular injury occurs in a relatively late stage of the process.

SPLANCHNIC HEMATOCRIT IN THE DOG DETERMINED FROM SIMULTANEOUSLY MEASURED SPLANCHNIC PLASMA AND RED CELL VOLUMES. *B. Cominsky, J. R. K. Preedy, R. Hays, H. O. Wheeler and S. E. Bradley.* Columbia Univ. College of Physicians and Surgeons, Presbyterian Hosp., New York, N. Y.

The hematocrit of blood in small vessels is less than that in large vessels, owing to lamination of flow. The hematocrit of the pooled total blood volume would therefore depend on the relative contribution of blood from vessels of different caliber.

With the development of a method for measuring splanchnic blood volume in the intact animal by regional retention and dilution of a tracer material, it is possible to measure the splanchnic hematocrit and thus to determine indirectly the distribution of blood within the splanchnic vasculature. Since in the dog the spleen is a large organ containing blood with a high hematocrit, measurements were carried out in both intact and splenectomized animals. In seven intact and eight splenectomized dogs anesthetized with nembutal® (30 mg. per kg.) splanchnic plasma volume (SPV) and splanchnic red cell volume (SRCV) were determined simultaneously by dilution of I-131 labelled albumin and P-32 tagged red cells, respectively. Splanchnic hematocrit (SHCT), calculated as SRCV/SRCV + SPV, was 79.4 ± 68.9 per cent of the peripheral arterial hematocrit in the intact and 71.8 ± 18 per cent in the splenectomized dogs. These figures do not differ significantly. In the determination of splanchnic blood volume, blood may be sampled from either a right or left hepatic vein. SHCT based on blood collected from the right was 73.9 ± 16.9 and from the left 77.0 ± 13.7 per cent of the peripheral arterial hematocrit, there being no significant difference between the two. These results indicate that the cell-rich blood of the spleen is not measured by the dilution technic used, and that the major portion of blood located in the splanchnic bed is located in small vessels, chiefly in the liver.

In five dogs (three splenectomized) simultaneous measurements of SPV, SRCV and SHCT from blood collected at the same time

from both right and left hepatic veins showed good agreement. This observation suggests that there is a uniform distribution of hepatic arterial and portal venous blood per unit mass of liver tissue.

PAPER ELECTROPHORETIC STUDIES OF SERUM PROTEINS IN VIRAL HEPATITIS. *Gerald R. Cooper*. Cummunicable Disease Center, Atlanta, Ga.

Specimens collected from forty-six patients with viral hepatitis have been analyzed by paper electrophoresis. The electrophoretic results were compared with seromucoid, C-reactive protein, bilirubin, cephalin flocculation and thymol turbidity values. Findings at the height of the disease in an average case showed an electrophoretic pattern with a distorted alpha-2 globulin peak, a slightly enlarged beta-globulin peak and a prominent increase in gamma globulin peak, a lowered seromucoid value, a one-plus C-reactive protein reading, and elevations in bilirubin, cephalin flocculation and thymol turbidity results. Persistently enlarged gamma globulin peaks were usually associated with continued elevated cephalin flocculation or thymol turbidity values. Six proved cases of posthepatitic cirrhosis gave abnormal results in all tests, especially paper electrophoresis.

SERUM GLYCOPROTEINS IN VIRAL HEPATITIS. *Fenton Schaffner, Arthur L. Scherbel and Ralph I. Lytle*. U. S. Naval Hosp. and Med. Research Unit No. 4, Great Lakes, Ill.

The serum glycoproteins were studied electrophoretically at weekly intervals in eleven patients with acute viral hepatitis from the first week of their illness until the time of discharge from the hospital and at the time of liver biopsy in three patients in whom viral hepatitis had persisted for three months or longer. The serum proteins were fractionated by paper electrophoresis. The strips were stained with bromophenol blue and treated with mineral oil and dioxan. Glycoproteins were determined on similar strips after staining with basic fuchsin. The serum gamma globulin was elevated early in the disease and returned to normal usually by the sixth week. High percentages of polysaccharides were associated with some of the gamma globulin elevations but in general the results were within normal limits and showed little change throughout the course of the disease. Beta globulin and associated polysaccharides remained normal. Alpha-2 proteins and polysaccharides were slightly elevated initially and became normal in one to two weeks. Albumin and alpha globulin were considered together. These proteins behaved as a mirror image of the gamma globulin while the polysaccharides dropped to low levels and returned to normal after the proteins. The total protein-bound carbohydrate appeared to be reduced, although this could not be well quantitated. The glycoprotein pattern differed from normal in that the amount of slower moving (gamma) carbohydrate increased while the more rapidly moving fraction decreased. This is in contrast to rheumatic fever in which the total glycoprotein was greatly increased, the greatest rise being in the more rapidly moving portions, especially both alpha globulins. In protracted hepatitis the albumin and alpha-1 polysaccharides were low and the gamma polysaccharides were high, although these changes were of the same magnitude as those in the acute stage. The only consistent feature histologically found in the three biopsy specimens was the persistence of hepatic inflammation. In general, it is felt that the behavior of the glycoproteins is a reflection of inflammation in the liver, as contrasted with changes noted in inflammation elsewhere.

SERUM COMPLEMENT IN HEPATOBILIARY DISEASE. *Emanuel E. Mandel and Kurt Lange*. Communicable Disease Center, Atlanta, Ga. and New York Medical College, New York, N. Y.

Conflicting reports concerning the serum complement titer in liver disease prompted its determination in twenty cases of cirrhosis (nineteen portal, one postnecrotic), fifteen of viral hepatitis and twenty-six of biliary obstruction which in sixteen patients was caused by neoplasm. The method, which gave a range of 1.8 to 3.6 units in twenty healthy subjects tested simultaneously, had previously been found by Lange consistently to yield low (less than 1 unit) or absent complement in acute glomerulonephritis and nephrosis. The range encountered in cirrhosis was 0.8 to 4.7 units (mean, 2.6), in hepatitis, 1.4 to 5.7 (3.2), in benign obstruction, 2.0 to 6.1 (4.0) and in cancer, 1.9 to 4.9 (3.7). Abnormally low complement was noted only in two cirrhosis patients dying of hepatic insufficiency. The majority of the group with cirrhosis and two of the patients with hepatitis had "extrahepatic" complications (pyelonephritis, pan-

creatitis, pneumonia), which may have counteracted a complement depression such as had been observed by Goldner and by Jordan in hepatocellular disease. Unusually high complement values encountered in all groups but especially in patients with benign obstruction presumably reflected the presence of an active infectious process. The present data fail to reveal any diagnostic utility of the test in liver disease, except for the occasional finding of complement diminution which may denote a grave prognosis.

TREATMENT OF FATTY LIVER WITH A HIGH FAT DIET. *Gordon M. Mindrum.* Cincinnati Gen. Hosp., Cincinnati, Ohio.

A high fat diet was used in the treatment of eight biopsy-proved cases of severe fatty liver. The daily diet averaged 120 gm. protein, 300 gm. carbohydrate and over 300 gm. fat. Stool fats averaged 29.5 per cent dry weight for twenty-four hours. Duration of treatment averaged 4.2 weeks. All patients showed progressive clinical improvement with reduction of liver size, clearing of ascites and edema, gain in strength and improved nutrition. Liver function showed improvement with total bilirubin dropping to within normal limits. Bromsulfalein retention decreased to near normal and serum albumin increased. Serum lipid values did not vary significantly. Serial liver biopsy specimens in three patients revealed clearing of visible liver fat in four to six weeks. This evidence suggests that patients with severe fatty livers can absorb and utilize large amounts of fat.

ROENTGENOLOGIC VISUALIZATION OF BILIARY DUCTS BY INTRAVENOUS INJECTION OF A NEW CONTRAST MEDIUM. *Raj K. Parida, Alexander J. Link, Julius Heydemann and Robert M. Kark.* Univ. of Illinois College of Med., Chicago, Ill.

The di-sodium salt of N,N-adypyl-bis(3-amino-2,4,6-triiodo)benzoic acid, a new roentgenologic contrast medium (chlorografin®), was used to study the biliary duct system in twenty-one patients. As corroborated by serial liver function studies in our patients, the toxicity of this compound is low when compared with other contrast media in use. Adequate roentgenologic visualization of the large bile ducts was obtained in fifteen of twenty-one patients following intravenous injection of the material. The six patients with non-visualization of the ducts had either severe hepatic dysfunction or air in the ducts due to previous surgery. The renal pelvis and calyces were visualized in several of the pictures, and this occurred more frequently in patients with known hepatic dysfunction.

The preparation appears to be a useful adjunct for the diagnosis of biliary tract diseases, especially for the study of intraductal pathology. Stones causing partial obstruction and strictures of the extrahepatic biliary ducts have been diagnosed by use of the dye and the observations were corroborated by surgery.

NAIL BEDS IN HEPATIC CIRRHOSIS. *Richard Terry.* Hektoen Inst. for Medical Research of Cook County Hosp., Chicago, Ill.

The nail beds may be divided into three zones, the half-moon, the main pink zone, and a narrow band running across the distal portion of the nail-bed, which is herein called the onychodermal band. The appearance of these three zones may be altered in hepatic cirrhosis.

On squeezing blood into the terminal phalanx, the normal main pink zone assumes a clear red color; in 'white nails' the redness is obscured by a whitish opacity similar in character to the half-moon. The opacity is in the nail-bed and not in the nail. Such white nails are not uncommon in clinical states but well marked examples occur most commonly in hepatic cirrhosis and in a few other disorders.

Normal half-moons have a barely perceptible pink tinge, but on occasion the half-moon becomes reddened. Such red half-moons, which are detectable at a distance of several feet, occur in cirrhosis although they are less common than white nails. Three patients with cirrhosis have been seen who had both red half-moons and white nails.

The normal onychodermal band is barely perceptible. It may, however, become opaque (with a faintly amber tinge) forming an easily detectable whitish band across the distal portion of the nail bed, 0.5 to 1.5 mm. in width. This appearance is rare, and only nine examples have been found by the author; of these, five were in cirrhosis.

The appearances described constitute physical signs occurring in hepatic cirrhosis which are occasionally of diagnostic value. It seems probable that they are of endocrine origin and that they are in the same category as spider nevi and other 'endocrine stigmata.'

Case Reports

Chronic Relapsing Pancreatitis with Associated Marked Eosinophilia and Pleural Effusion*

KERRISON JUNIPER, JR., M.D.

Boston, Massachusetts

MARKED eosinophilia associated with chronic relapsing pancreatitis is a rare phenomenon. The occurrence of a case in which eosinophilia and serum amylase were apparently correlated served as a stimulus to re-examine the records of sixteen other patients in which pancreatitis and eosinophilia occurred simultaneously. A review of the literature revealed no mention of eosinophilia occurring in association with pancreatitis.

CASE REPORT

First hospital admission: Patient W. F. H., a fifty-five year old white salesman, was admitted to another hospital on May 2, 1953, with a two year history of symptoms suggestive of congestive heart failure. There was also a history of epigastric pain with substernal radiation of several years' duration. Pain relationships were vague. All symptoms had become more intense for five months prior to admission. The immediate cause of admission was not clearly stated by the patient. There was a history of moderate alcohol intake. The patient had been hospitalized seven, nine and ten years previously for similar symptoms. On the last occasion he had been found to have hypertension and had received digitalis for a short time.

Examination revealed the patient to be afebrile and chronically ill, with a small left pleural effusion. Examination of the heart revealed it to be normal. The abdomen was protuberant with a fluid wave of questionable nature and with generalized tenderness, more marked in the left upper quadrant. The liver and spleen were not palpable.

Routine laboratory studies, liver function tests and stool examinations gave normal results. The initial impression was "possible cirrhosis of the liver and/or possible heart disease."

Four days after admission the patient became febrile and severe pleuritic pain developed in the lower left portion of the chest, with an increase in the left pleural effusion. Chest film revealed a density at the base of the left lung. At the same time symptoms of thrombophlebitis in the left leg appeared. A diagnosis of thrombophlebitis with pulmonary infarction was made. Serum amylase at this time was 220 units.† Signs of thrombophlebitis disappeared rapidly with treatment.

Eleven days after admission the abdomen became more distended and tympanitic, with tenderness localized to the left upper and left lower quadrants. The following day the tenderness was localized to the epigastrium and peristaltic sounds were absent. Signs of acute inflammation in the abdomen developed and laparotomy was performed thirteen days after the patient had been admitted. An inflammatory mass was found in the left upper quadrant of the abdomen extending down the left gutter to the level of the rectosigmoid junction, and cecostomy was performed. The liver appeared normal but adequate abdominal exploration was not possible because of dense adhesions and the patient's poor condition. Postoperative serum amylase was 800 units.

Mild abdominal pain and episodes of fever occurred postoperatively. On the eighteenth postoperative day the left pleural effusion had increased. Thoracentesis yielded 300 cc. of

† Amylase determinations were made by the modified Somogyi method[1] utilizing Nelson's method for determination of the blood glucose.[2] Normal values at this hospital range up to 200 units.

* From the Medical Service, V. A. Hospital, and Dept. of Medicine, Emory Univ. School of Medicine, Atlanta, Ga.

sterile, straw-colored fluid containing 800 units of amylase, 300 white blood cells and 40,000 red blood cells per ml. Two days later an additional 950 cc. of similar pleural fluid was removed, following which the fluid did not reaccumulate.

During the latter period of hospitalization, productive cough with some blood-streaking of the sputum, and night sweats. At this time he gave a five-year history of recurrent gnawing epigastric pain, and sharp pain aggravated by deep breathing in the left upper abdominal quadrant and left chest. Pain relationships were

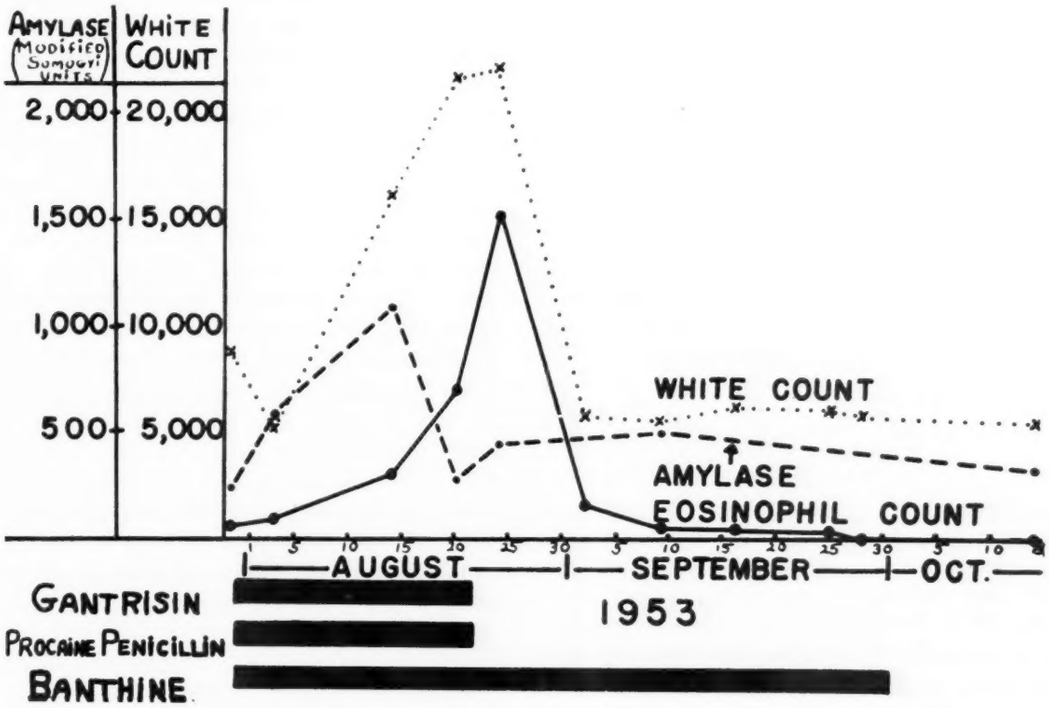

FIG. 1. Serum amylase and blood eosinophil levels during the second hospitalization period.

upper and lower gastrointestinal series gave normal results. Serial laboratory studies showed a white blood count of 5,300 with no eosinophilia on admission, and a rise of the eosinophil count to 550 in 11,000 white blood cells five days after admission.* Three days after surgery the white blood count was 15,000 with 750 eosinophils per ml. The patient was discharged two months after admission with a final diagnosis of acute pancreatitis.

Second hospital admission: The patient was admitted to this hospital on July 30, 1953, thirty-five days after discharge from his first hospitalization, complaining of dyspnea, chest pain and vomiting of several days' duration. During the preceding three weeks he had had a slightly poor, although alcohol had been noted to aggravate and milk to relieve the gnawing pain. He had had nausea but only occasional vomiting with these attacks of pain.

The patient was acutely ill, although afebrile, with moderate left-sided pleural effusion. The heart was normal. The abdomen was generally tender, especially in the left upper quadrant, where an ill defined mass was palpated. The liver and spleen were not palpable.

Amylase levels, white blood cell, and eosinophil counts are shown in Figure 1. Of particular note are the maximum white blood cell count of 22,150 taken during the fourth week of hospitalization and the marked eosinophil counts of 11,935 and 15,284 per ml. during the third and fourth weeks of hospitalization. Laboratory tests for tuberculosis and intestinal parasites gave negative results. Several serologic tests for syphilis gave positive results on admission but reverted to normal after the acute illness had subsided. Bromsulphalein retention

* Total eosinophil counts in this paper were estimated by multiplying the total white blood cell count by the percentage of eosinophils found on the routine differential count. In a few instances direct total counts were done to verify the degree of eosinophilia found. An eosinophil count of 200 per ml. was considered the upper limit of normal.

was 20 per cent in one-half hour (5 mg. dye per kg. of weight), serum bilirubin 2.1 mg. per cent, and serum proteins 7.2 gm. per cent with 3.9 gm. of albumin and 3.3 gm. of globulin. Flocculation tests of liver function gave normal results. Serum amylase was 237 units. Electrocardiogram was normal.

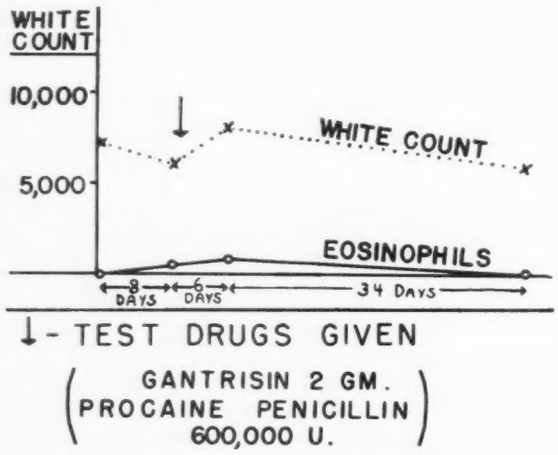

FIG. 2. Sensitivity study.

On admission 400 cc. of thin, sterile, straw-colored fluid were removed from the left pleural cavity. This fluid contained 5.8 gm. per cent protein, 2,375 white blood cells and 5,000 red blood cells per ml. Differential count of the pleural fluid cells showed 2 per cent polymorphonuclears, 8 per cent lymphocytes, 1 per cent eosinophils, 1 per cent basophils, 85 per cent histiocytes and 3 per cent mesothelial cells.

During the first week of hospitalization the patient was febrile with temperatures as high as 101°F. He received procaine penicillin and gantrisin® for the first twenty-one days, and banthine® during the entire period of hospitalization. During the last five weeks there was gradual improvement with resolution of the pleural effusion.

One month after admission a repeat bromsulphalein test gave normal results. Upper and lower gastrointestinal and gallbladder series gave normal results. Serial chest films showed gradual resolution of the pleural effusion with no evidence of a parenchymal lesion. The highest serum amylase level occurred two weeks after admission and was 1,094 units. The patient was discharged ten weeks after admission with a diagnosis of chronic relapsing pancreatitis.

The patient has been followed as an outpatient for a period of one year, during which time he has had approximately one attack per month of abdominal pain with nausea and vomiting, each attack lasting about five days. Follow-up chest films have shown no return of the pleural effusion, and serum amylase levels have remained within normal limits. A very slight eosinophilia has been noticed occasionally.

In order to investigate the possibility of a drug sensitivity, the patient was studied during a relatively asymptomatic period six months after his discharge from the hospital. Unfortunately, patient cooperation was poor and laboratory tests could not be done at the desired times. Control eosinophil counts were made and the patient given 600,000 units of procaine penicillin intramuscularly in a single dose and 4 gm. of gantrisin orally over a forty-eight-hour period. Figure 2 demonstrates the results of the sensitivity test. At no time during the test did any symptoms or signs of an allergic reaction develop. It was unfortunate that the second control eosinophil count had risen to an abnormally high value (600 per ml.). The additional rise of only 200 eosinophils after drug administration seemed insignificant in comparison with the 527 rise which occurred between the control counts. The total eosinophil rise during the test seemed particularly insignificant in relation to the maximum eosinophil count of 15,284 per ml. which appeared during the acute illness. The conclusion drawn from this test was that a drug reaction to either procaine penicillin or gantrisin was an unlikely cause of the eosinophilia which occurred in association with the acute attack of pancreatitis.

REVIEW OF SIXTEEN CASES OF PANCREATITIS WITH EOSINOPHILIA

The relationships found in the case presented suggested a review of other cases of pancreatitis. The serum amylase determinations done at this hospital during the previous nineteen months were examined and the records revealed that sixty patients had had amylase values of 200 or more units. Of these forty-two also had total eosinophil counts of over 250 per ml. There was adequate clinical data on sixteen of this group with eosinophilia to substantiate a definitive diagnosis of pancreatitis of either the acute or chronic type. Eight patients had eosinophil counts of over 500 per ml., and those of two patients were above 1,000 per ml. In no case, however, was there any obvious relationship between the activity of the disease and eosinophilia, although a mild-to-marked eosinophilia

was present. There were no other obvious causes of the eosinophilia in this group. The type of study done and the small number of cases found did not permit evaluation of the significance of eosinophilia generally in pancreatitis.

COMMENTS

The eosinophilia which appeared in this patient during the second period of hospitalization was very striking. Intestinal parasites, first thought to be the cause, could not be found. The course of the disease made periarteritis, trichinosis and malignancy (other common causes of marked eosinophilia) seem unlikely. The possibility of a drug reaction was considered because the patient had received procaine penicillin and gantrisin during the time he had eosinophilia. The drug sensitivity test, however, made this seem unlikely.

Plotting the serum amylase values and total eosinophil counts (Fig. 1) revealed an interesting relationship. It was noted that ten days after the peak amylase value (representing in this case the more acute period of the disease process) the maximum eosinophil response appeared. This lag resembled the ten to fourteen-day period frequently seen before the delayed systemic response manifests itself after exposure to an allergen. This is not an indication that the eosinophilia in this patient was the result of an allergen (such as altered pancreatic proteins) released during the acute inflammatory process, although it remains a possibility. Whatever the cause, it was the impression of those associated with this case that the eosinophilia was directly related to the acute pancreatitis. A third severe attack of pancreatitis has not occurred to date in this patient and consequently further observations on eosinophilia and acute pancreatitis have not been possible.

This case also demonstrates the difficulty frequently encountered in the initial diagnosis of acute pancreatitis. That pleural and peritoneal effusions occur in conjunction with acute pancreatitis is well known. Less well known is the fact that such effusions may contain increased amounts of amylase and that such levels may be higher than blood serum values and remain elevated longer. The presence of pleural effusion containing 800 units of amylase in this case was of particular interest. Various mechanisms have been suggested as the cause, varying from inflammation of the diaphragmatic pleura by adjacent abdominal inflammation or a subdiaphragmatic abscess, to lymph drainage of high enzyme content from the abdomen through the diaphragm into the pleural cavity. The presence of large amounts of amylase in the pleural fluid makes the latter theory seem plausible, although it is possible that diffusion from the blood serum also may occur. Reports that the serum-amylase levels have been found to be lower than the pleural fluid content at the same time make this less likely. However, there has not been adequate investigation to rule out the possibility that the pleural fluid amylase content diffused from the blood serum at an earlier time and merely persisted after the blood amylase level had fallen.[3–9]

SUMMARY

A case of chronic relapsing pancreatitis with pleural effusion on the left side is presented. During an acute exacerbation marked eosinophilia was observed which appeared to be related to the activity of the inflammatory process. Eosinophilia of a mild-to-marked degree was found in sixteen other cases of definite pancreatitis but no obvious relationship between eosinophilia and degree of activity (including amylase values) was found. No mention of a similar relationship between eosinophilia and pancreatitis was found in the literature.

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Aneurysm of the Left Coronary Artery*

MILTON TELLEM, M.D. *and* A. I. RUBENSTONE, M.D.
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ONLY fifty cases of localized aneurysm of the coronary artery have been reported in the literature. Bougon in 1912 was the first to describe such a finding. Packard and Wechsler[1] in 1929 reported a total of twenty-nine cases, including one of their own. They classified these cases according to an arteriosclerotic or mycotic-embolic etiology. Scott[2] reported another case in 1948 and in a review of the literature compiled forty-seven cases. Since Scott's paper appeared only single case reports by Sarkisian[3] in 1950, Rukstinat[4] in 1952 and Colbeck and Shaw[5] in 1954 have been reported, thus bringing the total number of reported localized coronary aneurysms to fifty.

CASE REPORT

A sixty-nine year old white woman, markedly obese, was admitted on June 1, 1954, complaining of progressive severe substernal pain. Marked dyspnea and ankle edema were present. This admission was the last of many beginning in 1942 for hypertension, congestive failure and symptoms of coronary insufficiency. No history of rheumatic fever, syphilis, subacute bacterial endocarditis or myocardial infarction was present. On this last admission the patient's blood pressure was 130/70 and her pulse was 75. Her usual pressure was about 200/100. She was markedly dyspneic, pale and sweaty. Fine moist rales were heard bilaterally in both lung bases and the heart sounds were of regular rhythm and barely audible. The abdomen was very obese; no viscera or masses were definitely palpable. A +2 pitting edema of the ankles and feet was noted. An x-ray of the chest showed left ventricular enlargement and a small amount of fluid at the left base. A review of previous electrocardiograms revealed progressive coronary insufficiency. An electrocardiogram taken during the last twenty-four hours of the patient's life showed anoxia of the anterior wall of the left ventricle and auricular fibrillation. These observations were not present in previous electrocardiograms. The course in the hospital was marked on one occasion by a period of unconsciousness and transient left hemiplegia which cleared in one and one-half hours. Recurrent bouts of chest pain with left shoulder radiation also took place. Three days before death the patient became febrile and suffered severe nausea and vomiting. Severe pulmonary edema developed on June 30 and the patient expired.

At autopsy, marked bilateral pulmonary edema was present. The heart weighed 500 gm.; all chambers were moderately dilated. The left ventricular wall measured 16 mm. and the right ventricular wall measured 8 mm. The mitral and aortic valves showed moderate sclerosis at the free edges but did not show evidence of rheumatic heart disease or subacute bacterial endocarditis. The entire aorta showed moderate involvement by atherosclerosis but no evidence of syphilis was noted. On sectioning the cardiac muscle focal streaky areas of fibrosis were revealed. Both coronary ostia were adequately patent. The coronary arteries presented a balanced distribution with slight focal atherosclerotic involvement.

Two centimeters distal to the ostium of the left coronary artery a small coronary branch 1 mm. in diameter was observed which coursed downward to the right. This branch, 1½ cm. from its origin, led to a saccular aneurysm measuring 5 cm. in diameter which reached to, overlaid and apparently compressed the main anterior descending branch of the left coronary artery. The aneurysm contained an organized peripheral laminated blood clot with central fresh hemorrhagic material. The wall of the aneurysm measuring 1 mm., was markedly thin and showed focal points of ulceration and

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calcification. From its position the aneurysm could have pressed down upon and thus have been responsible for intermittent occlusion of the anterior descending coronary artery. (Fig. 1.)

Microscopic sections of the aneurysm wall revealed destruction of the inner elastic membrane. Necrotic atheromatous material and foci of calcification were noted on the inner aspect of the wall. One area revealed a site of definite bone formation. The media was markedly fibrosed in many areas. From these histologic features it is apparent that the aneurysm was not of recent origin.

Histologic sections of the major coronary vessels revealed only minimal atherosclerosis. Several compressed coronary branches were noted in the vicinity of the aneurysm. The heart muscle itself showed numerous disseminated areas of focal fibrosis and moderate fiber hypertrophy. (Fig. 2.)

The final diagnoses of the pathologist were congestive failure secondary to hypertensive arteriosclerotic cardiovascular disease, and an arteriosclerotic aneurysm of the main left coronary artery.

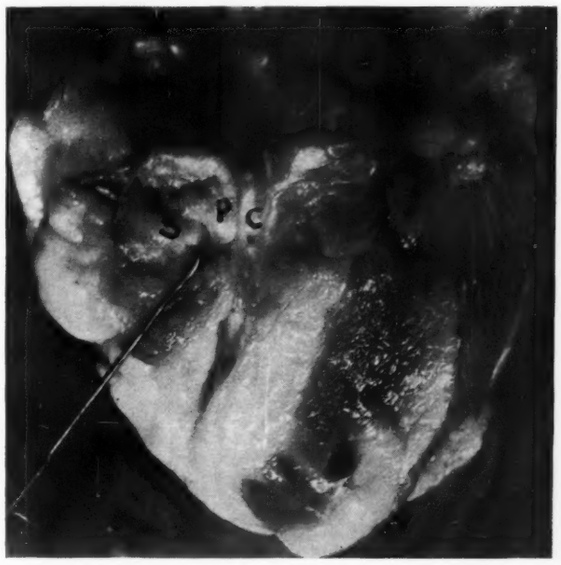

FIG. 1. Aneurysm incised to show its straddling position over the anterior descending coronary artery. A, wall of aneurysm; C, anterior descending coronary artery; P, probe in lumen of small coronary branch; S, sac of aneurysm.

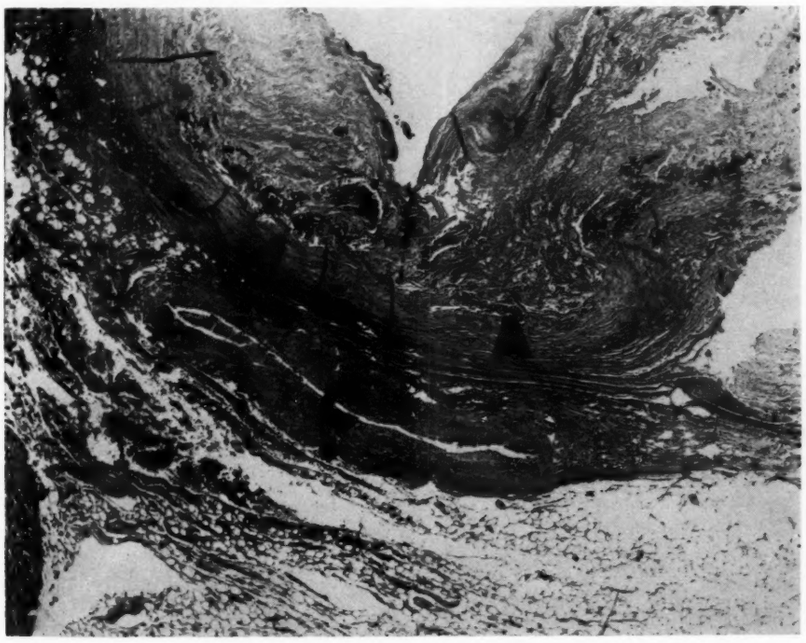

FIG. 2. Wall of aneurysm overlying and compressing coronary artery branch. A, wall of aneurysm; C, compressed coronary artery branch.

COMMENTS

Scott classified the aneurysms in his compilation as localized and diffuse. The localized aneurysms were further subclassified etiologically as congenital, fifteen patients; mycotic-embolic, twelve; arteriosclerotic, six; syphilitic, six; purely mycotic, one; rheumatic, one; possible periarteritis nodosa, two; and unclassified, four. The left coronary artery was involved in twenty-seven patients, the right coronary artery in eleven, and both were involved in six pa-

tients. In three patients the sites of involvement were unstated. The commonest causes of death in the localized aneurysm were coronary thrombosis, congestive heart failure and coronary rupture.

In reviewing the literature it is found that a single aneurysm of the coronary is usually located immediately distal to the coronary orifice within the first inch of the origin of the vessel. In mycotic-embolic aneurysms the sac usually contains infected embolic material. The infection first involves the intima and spreads through the media and adventitia. Leukocytic infiltration and destruction of the internal elastic membrane ensue with secondary destruction of the media. Pure mycotic aneurysms are usually associated with septicemia. Aneurysms due to arteriosclerosis show destruction of the internal elastic lamina at the site of the atheromatous plaque along with destruction and atrophy of the media. The three single case reports since Scott's paper all occurred against an arteriosclerotic background. It is interesting to note in our case report that although the aneurysm was also on an arteriosclerotic basis, it was associated with minimal arteriosclerotic involvement of the remainder of the major coronary branches. This observation has been previously noted by Scott. It is possible therefore that a factor contributing to the progressively severe angina and cardiac failure experienced by our patient during her last year of life may have been external pressure of the aneurysm on the left anterior descending coronary branch. This view is further supported by the widespread myofibrosis and lack of any occluding atherosclerosis elsewhere.

SUMMARY

A case of localized aneurysm of the left coronary artery is presented. This is believed to be the fifty-first case reported in the literature. Ten of these aneurysms, including the one herein reported, were on an arteriosclerotic basis.

Death from aneurysm is usually due to congestive failure, coronary thrombosis or rupture. In our study it is postulated that intermittent occlusion of the left anterior descending coronary artery by external pressure from the overlying aneurysm may have contributed to the terminal manifestations of congestive heart failure.

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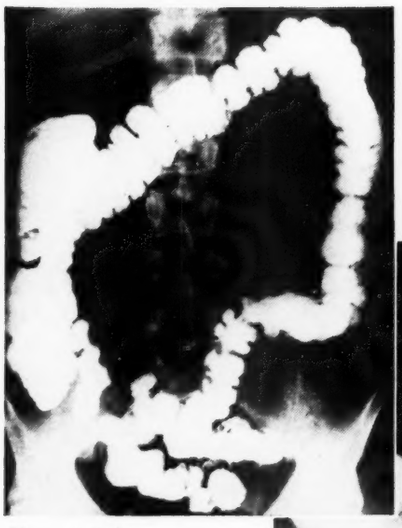

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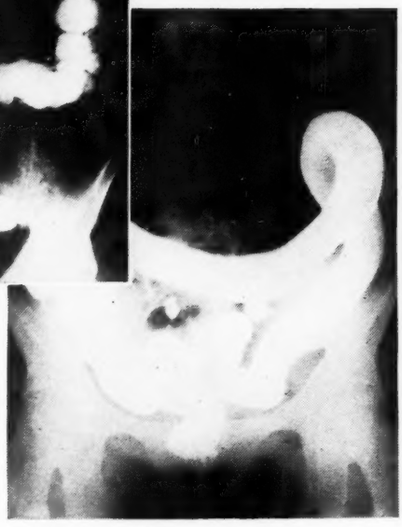

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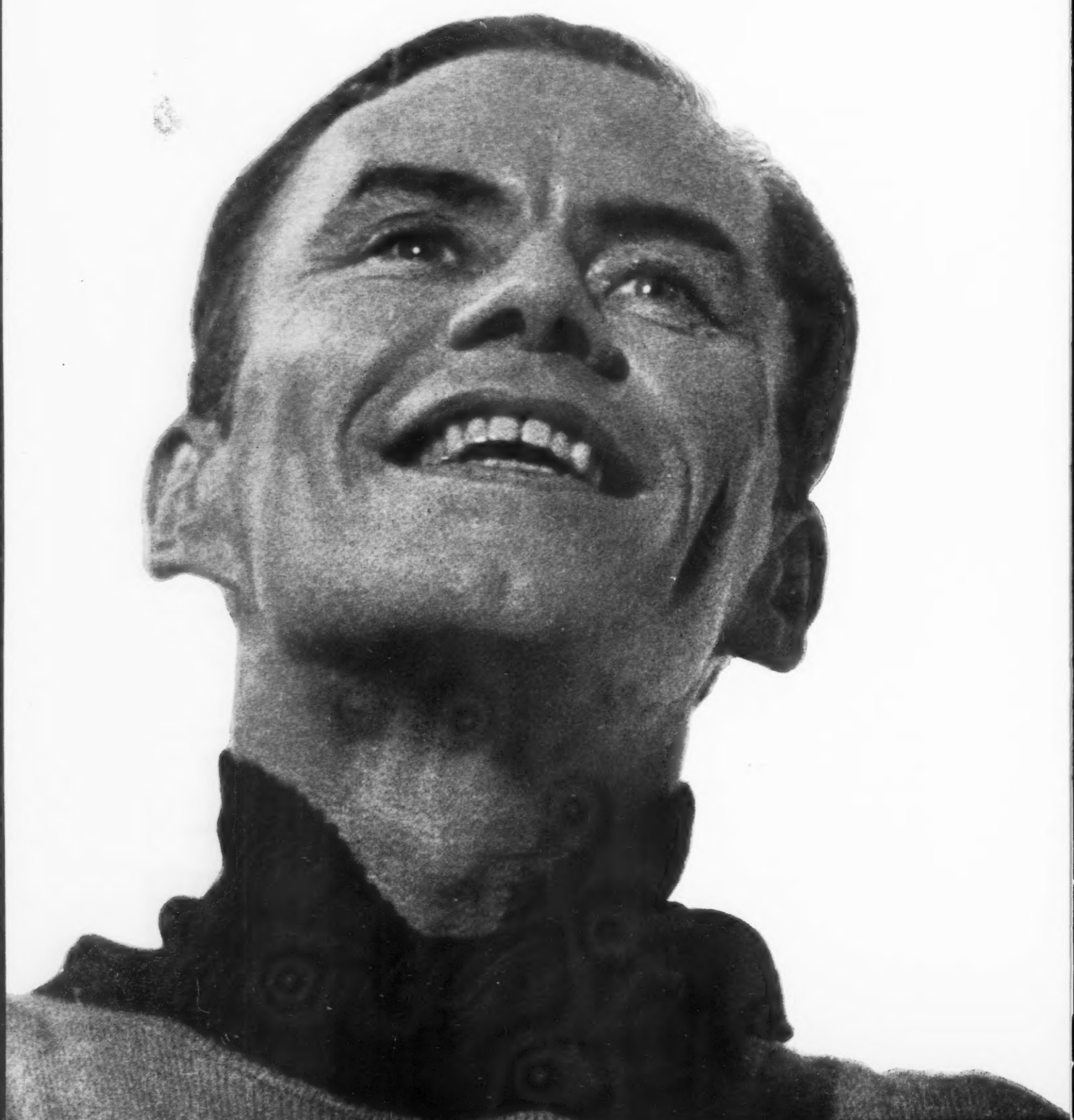

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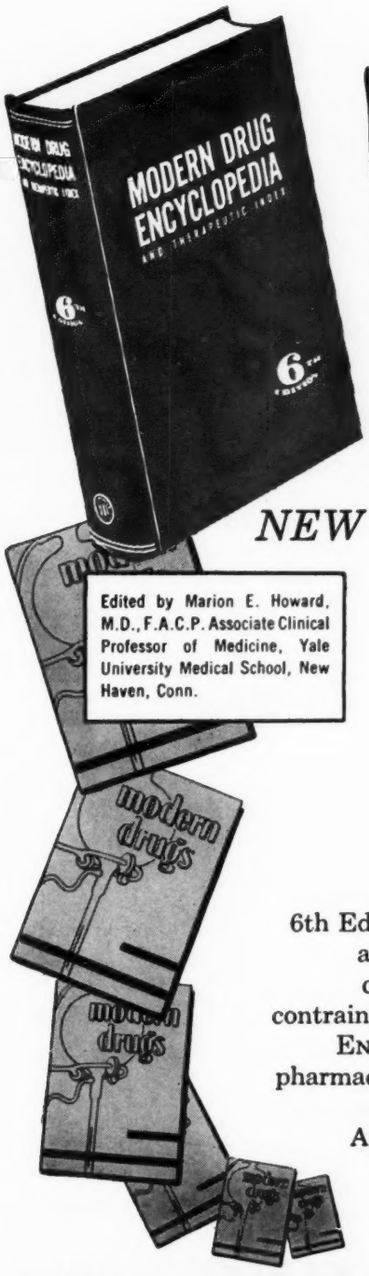

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**Foreign $18.00 **Includes three-year supplementary service at $3 per year.

M105

MAXIMUM SAFE ANALGESIA

(free from risk of addiction)

in whatever potency each patient may require

By facilitating the optimal analgesic medication of each patient without risk of addiction, PHENAPHEN and PHENAPHEN WITH CODEINE have proven their wide range of clinical usefulness — for cases of simple headache to many of late cancer.

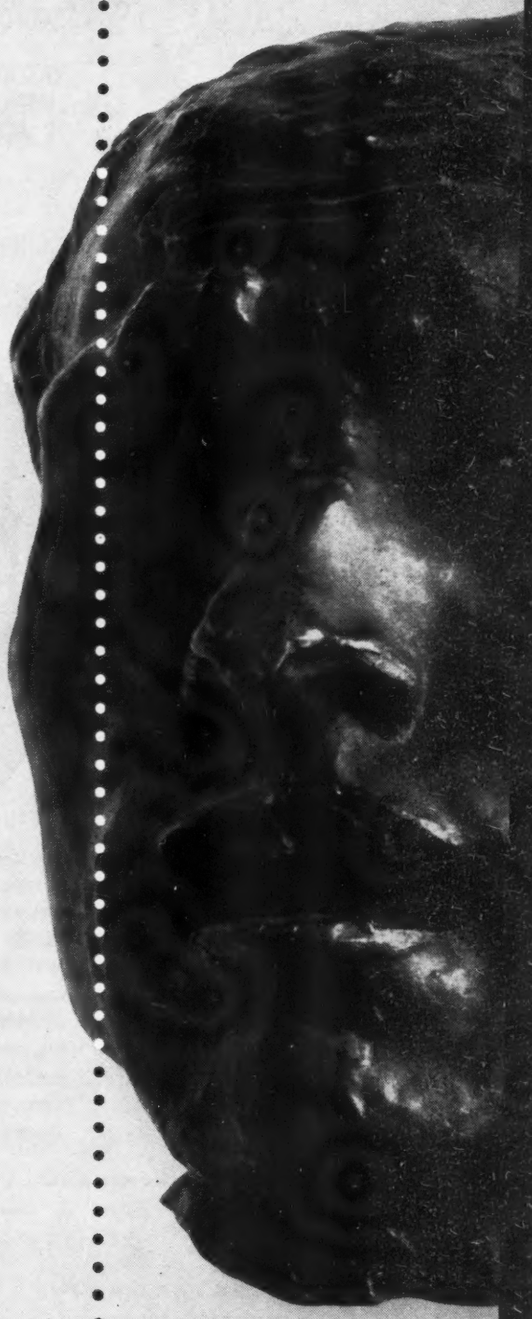
True pharmacodynamic synergism enhances the therapeutic potency of each of the 4 forms available for discriminating prescription:

PHENAPHEN
— basic non-narcotic formula
Each brown and white capsule contains:
Acetylsalicylic acid (2½ gr.).....162 mg.
Phenacetin (3 gr.).....194 mg.
Phenobarbital (¼ gr.).....16.2 mg.
Hyoscyamine sulfate ($\frac{1}{2000}$ gr.)..0.031 mg.

Phenaphen No. 2
PHENAPHEN
with CODEINE PHOSPHATE ¼ GR.
Each black and yellow capsule contains:
The basic phenaphen formula plus
Codeine phosphate (¼ gr.).....16.2 mg.

Phenaphen No. 3
PHENAPHEN
with CODEINE PHOSPHATE ½ GR.
Each black and green capsule contains:
The basic phenaphen formula plus
Codeine phosphate (½ gr.).....32.4 mg.

Phenaphen No. 4
PHENAPHEN
with CODEINE PHOSPHATE 1 GR.
Each green and white capsule contains:
The basic phenaphen formula plus
Codeine phosphate (1 gr.).....64.8 mg.



A. H. ROBINS CO., INC. • Richmond 20, Virginia

Ethical Pharmaceuticals of Merit since 1878

Phenaphen® Robins

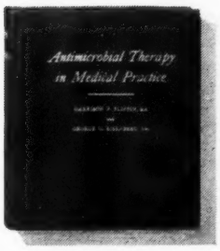
Phenaphen® with Codeine

Latest data on effectiveness of Furadantin®

brand of nitrofurantoin, Eaton

in urinary tract infections

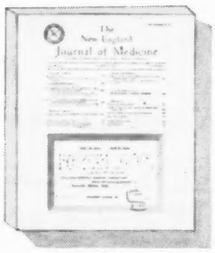
Investigators:



Latest data on effectiveness of Furadantin

Flippin, H. F., and Eisenberg, G. M.: Antimicrobial Therapy in Medical Practice, Philadelphia, F. A. Davis Co., 1955, p. 40.

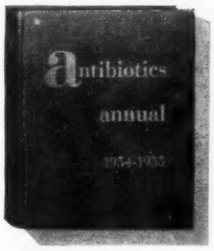
Clinical studies have demonstrated rapid clinical response in cases of cystitis and pyelonephritis, including infections caused by refractory organisms.



Trafton, H. M., et al.: New England J. Med. **252:** 383, 1955.

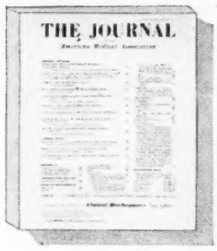
13 acute cases . . . 6 appeared cured . . . 6 markedly improved with no relapses.

36 chronic infections: 30 showed symptomatic improvement, frequently within 24 hours.



Beutner, E. H., et al.: Antibiotics Annual, 1954-1955, New York, Medical Encyclopedia, Inc., 1955, p. 988.

30 chronic urinary tract infections: Of 47 strains of bacteria isolated from these patients, 29 strains (62%) were eradicated by Furadantin.



Hasen, H. B., and Moore, T. D.: J.A.M.A. **155:** 1470, 1954.

Of patients with acute urinary tract infections, 95.7% were benefited. Patients with chronic infections and those with organic or obstructive lesions were benefited in 82% of cases.

Dosage — average adult: four 100 mg. tablets daily, 1 tablet with each meal and 1 tablet on retiring, with food or milk.

Furadantin tablets, 50 and 100 mg. in bottles of 25 and 100. Furadantin Oral Suspension (5 mg. per cc.), bottle of 4 fl.oz. (118 cc.).

EATON LABORATORIES
NORWICH • NEW YORK

THE NITROFURANS—A UNIQUE CLASS OF ANTIMICROBIALS O_2N PRODUCTS OF EATON RESEARCH

Syrup and oral tablets. Each teaspoonful or tablet of HYCODAN contains 5 mg. dihydrocodeinone bitartrate and 1.5 mg. Mesopin.* May be habit-forming. Average adult dose, 1 teaspoonful or 1 tablet after meals and at bedtime.

Hycodan®

(Dihydrocodeinone with Homatropine Methylbromide)

*Homatropine methylbromide

BETTER THAN CODEINE **FOR COUGH**[1]

FASTER • LONGER-LASTING • MORE THOROUGH

BETTER THAN CODEINE *PLUS* APC **FOR PAIN**[2]

Percodan®†

(Salts of Dihydrohydroxycodeinone and Homatropine, plus APC)

Scored, yellow oral tablets. May be habit-forming. Average adult dose, 1 tablet q. 6 h.

your best bet!

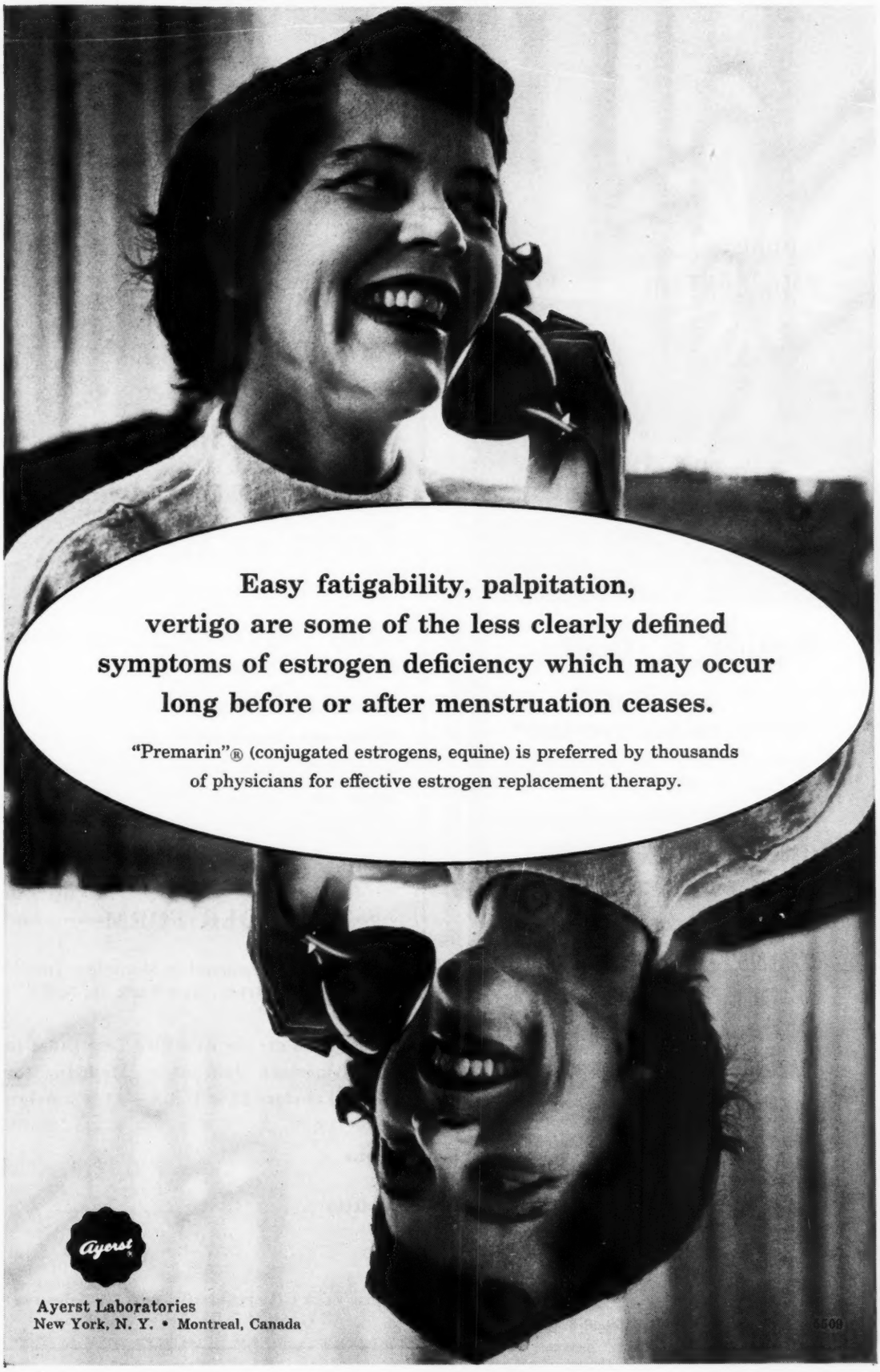
Literature? write

ENDO PRODUCTS INC., RICHMOND HILL 18, NEW YORK

1. Hyman, S., and Rosenblum, S. H.: Illinois M. J. 104:257, 1953.
2. Piper, C. E., and Nicklas, F. W.: Indust. Med. 23:510, 1954.

†U. S. Pat. 2,628,185

Endo®


Easy fatigability, palpitation,
vertigo are some of the less clearly defined
symptoms of estrogen deficiency which may occur
long before or after menstruation ceases.
"Premarin"® (conjugated estrogens, equine) is preferred by thousands
of physicians for effective estrogen replacement therapy.
Ayerst
Ayerst Laboratories
New York, N. Y. • Montreal, Canada
5509

Meat...

and America's Freedom from Protein Malnutrition

America is relatively free from extreme forms of protein malnutrition, since meat and other sources of protein make up a substantial portion of the national dietary. On the other hand, peoples of tropical lands, whose dietary provides little meat or other high quality protein, suffer widespread protein deficiency.[1]

In its severe form, protein malnutrition is "characterized by generalized edema, chronic bulky diarrhea with remnants of undigested food in the feces, hypoproteinemia, and atrophy of small intestinal mucosa and of the pancreatic acini, as well as by fatty infiltration of the enlarged liver."[1] Other characteristics are changes in pigmentation and ulceration of the skin, and depigmentation of the hair. "Mental apathy and often peevishness are outstanding psychological attributes of children with severe protein malnutrition."[1]

Clinical sequelae of protein malnutrition include kwashiorkor and liver disease.[1] In kwashiorkor the caloric intake may approximate normal, but the dietary protein is less than the necessary minimum in quality and quantity. Many tropical diets supply 10 to 15 per cent of the calories in the form of vegetable protein. Kwashiorkor may follow infections, especially of the gastrointestinal tract. Diets below 10 per cent in protein calories lead to frank protein malnutrition, including signs and symptoms of kwashiorkor.

In 5,000 autopsies on African natives no normal liver was found.[2] Infantile cirrhosis with ascites, prevalent in Jamaica, is believed to result from protein deficiency. Toxic, postnecrotic cirrhosis in children in India occurs concomitantly with low intake of protein, especially animal protein.

Government estimations indicate that 156 pounds of meat (carcass weight: beef, veal, lamb, and pork) were consumed per capita in the United States in 1954.[3] Providing large amounts of protein, vitamin B complex, and essential minerals, meat contributes valuably to the good nutrition of the American people. Meat is outstanding both in the amount and in the biologic quality of its protein.

---

1. Gyorgy, P.: On Some Aspects of Protein Nutrition, Am. J. Clin. Nutrition 2:231 (July-Aug.) 1954.

2. Davies, J.N.P.: Kwashiorkor. Trans. Ninth Conf. on Liver Injury, Josiah Macy, Jr. Foundation, 1950, p. 109.

3. The National Food Situation, Washington, D. C., Agricultural Marketing Service, United States Department of Agriculture, Oct. 29, 1954, p. 4.

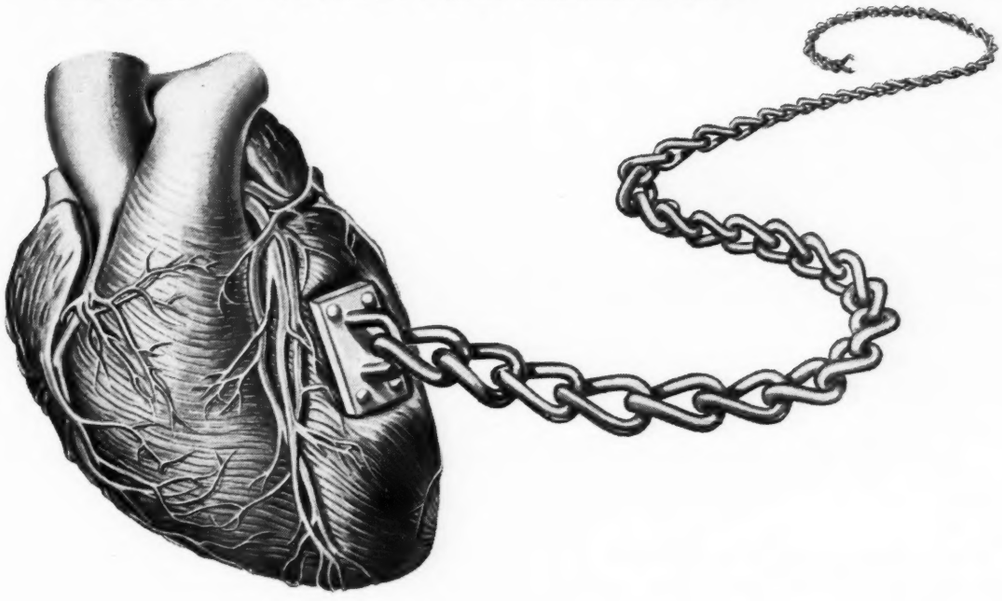
The nutritional statements made in this advertisement have been reviewed and found consistent with current medical opinion by the Council on Foods and Nutrition of the American Medical Association.

American Meat Institute

Main Office, Chicago... Members Throughout the United States

in your anginal patient...

break the chain of "heart-consciousness"



Your anginal patient can be freed from his "heart-consciousness" for a wider range of activities by the daily administration of Nitralox which aids in protecting him against the bodily and emotional factors which so often precipitate anginal seizures. Nitralox generally lessens the frequency and severity of attacks, will often lower nitroglycerin requirements, increase exercise tolerance and improve the electrocardiogram.

In anginal patients with hypertension and tachycardia, Nitralox has the added advantage of reducing the blood pressure and slowing the pulse. It has no such effects in normotensives with normal heart rates.

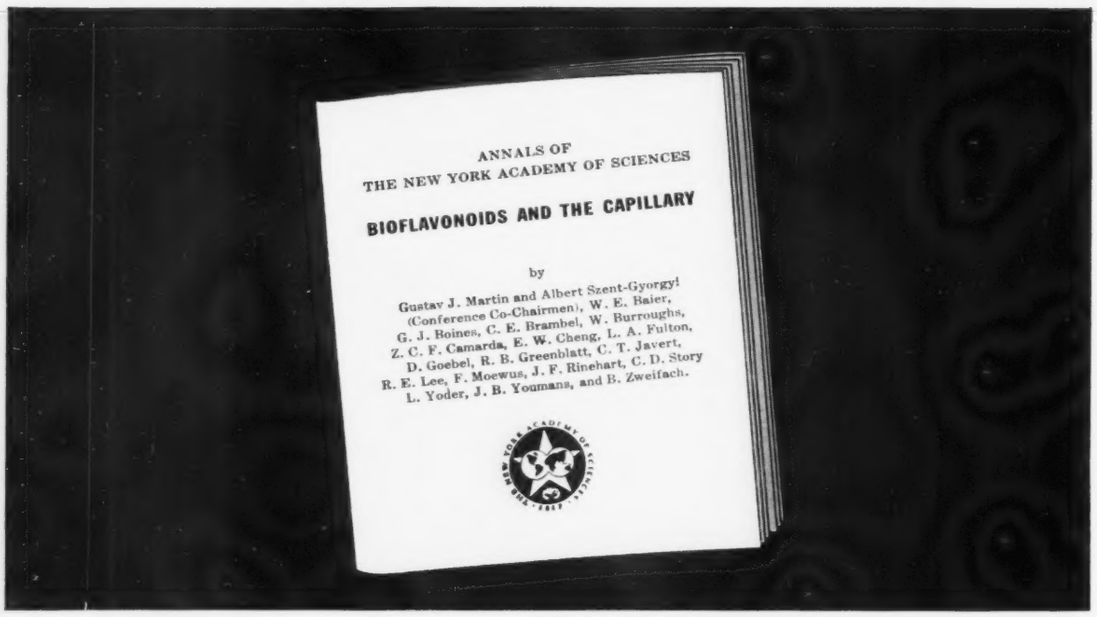
Nitralox combines a coronary vasodilator with prolonged action (10 mg. pentaerythritol tetranitrate – PETN) with a nonbarbiturate tranquillizing and bradycrotic agent (1 mg. purified mixed Rauwolfia alkaloids – the alseroxylon fraction) and is intended for long-term prophylactic therapy. While some patients experience beneficial effects within 24-48 hours, it takes about two weeks before Nitralox produces its full effect from the recommended dosage of 1-2 tablets q.i.d. before meals, and at bedtime.

NITRALOX

for long-range management of anginal attacks

Nitralox is a DORSEY preparation

Smith-Dorsey • Lincoln, Nebraska • A Division of The Wander Company



Latest report on the values of the bioflavonoids in health and disease

This free monograph of the recent Bioflavonoid Conference should be read by every doctor.

A recent symposium, bringing together current thoughts and findings on the chemistry, biochemistry and biological actions of the bioflavonoids, has supplied further evidence of the important role played by the flavonoid materials in both health and disease.

Focal point of the discussions was the value of the flavonoids to the capillary system... how they aid in the maintenance of normal capillary integrity and aid in the treatment of impaired capillary function.

Other papers and discussions covered the application of the bioflavonoids to the management of rheumatic fever, habitual abortion, poliomyelitis and their role in anticoagulant therapy. Discussions emphasized the importance of the relationship of the bioflavonoids with vitamin C.

Complete information on the symposium proceedings, monograph of the talks and notes on the discussions are available on request. Write Sunkist, Box 2706, Terminal Annex, Los Angeles 54, California.

The flavonoids are widely distributed in nature but are especially abundant in fresh oranges and lemons.

Fresh lemon juice has been established as an important source. In oranges the bioflavonoids are found mainly in the cell walls and fibrous tissues of the fruit rather than the juice. The whole peeled orange contains 10 times as much bioflavonoid as the finely strained juice alone.

The bioflavonoids are another reason for the increasing interest in citrus in its natural form... fresh.

Sunkist Oranges · Lemons

Sunkist citrus is recognized as the finest in any market... anywhere.

safe, reliable sedation

(non-barbiturate)

allays apprehension

eases onset of sleep

remarkably well tolerated by both children and adults

DORMISON,® brand of methylparafynol.

DO-J 52

Serpasil®

(reserpine CIBA)

Elixir

Sedation without hypnosis

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The high degree of solubility of "Thiosulfil" combined with its high bacteriostatic activity and low acetylation rate insure rapid and effective action with virtually no side effects.

"THIOSULFIL"®

Brand of sulfamethylthiadiazole

safest, most effective sulfonamide for urinary tract infections

Ayerst Laboratories • New York, N. Y. • Montreal, Canada

Ayerst

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establishing
desired
eating
patterns

Obedrin®

and the 60-10-70 Basic Plan

Correct medication is important in initiating control that leads to development of good eating habits, essential in maintaining normal weight.[1,2,3]

Obedrin contains:

- Methamphetamine for its anorexigenic and mood-lifting effects.
- Pentobarbital as a corrective for any excitation that might occur.
- Vitamins B_1 and B_2 plus niacin for diet supplementation.
- Ascorbic acid to aid in the mobilization of tissue fluids.

Obedrin contains no artificial bulk, so the hazards of impaction are avoided. The 60-10-70 Basic Plan provides for a balanced food intake, with sufficient protein and roughage.

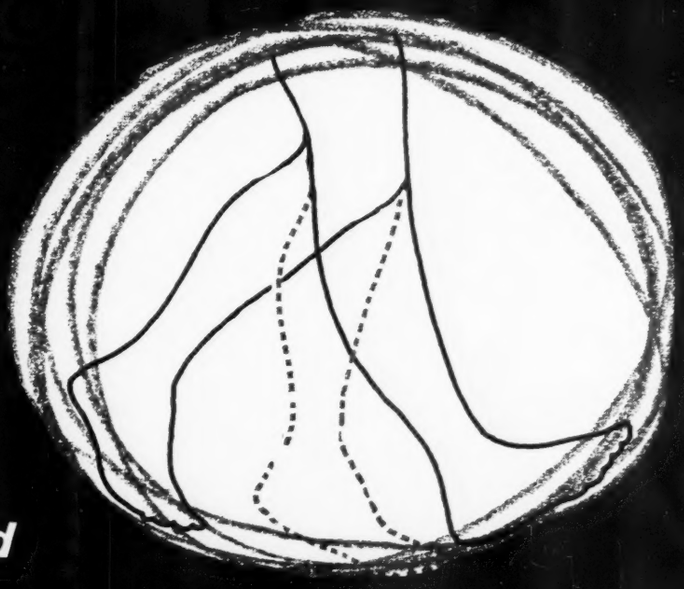
Formula:

Semoxydrine HCl (Methamphetamine HCl) 5 mg.; Pentobarbital 20 mg.; Ascorbic acid 100 mg.; Riboflavin 1 mg.; Niacin 5 mg.

1. Eisfelder, H.W.: Am. Pract. & Dig. Treat., 5:778 (Oct.) 1954. 2. Sebrell, W.H., Jr.: J.A.M.A., 152:42 (May) 1953. 3. Sherman, R.J.: Medical Times, 82:107 (Feb.) 1954.

Write for 60-10-70 Menu pads, Weight Charts, and samples of Obedrin.

THE S. E. MASSENGILL COMPANY
BRISTOL, TENNESSEE



range of motion rapidly increased

in Rheumatoid Arthritis

Sterane*

the most potent anti-arthritic

3 to 5 times more potent than hydrocortisone or cortisone

notably free of major hormonal side effects such as edema due to sodium and water retention, hypopotassemia, and hypertension

seldom requires low-sodium diets or potassium supplements in patients without cardiac complications when given in usual therapeutic dosage

preliminary findings,[1] based on the measuring of pituitary ACTH suppression potency of various corticoids, appear to indicate that STERANE is 20% more potent than the cortisone analog, prednisone

supplied: in white, scored 5 mg. tablets in the familiar Pfizer oval shape

1. Forsham, P. H., et al.: Paper presented at First Internat. Conf. on Prednisone and Prednisolone, New York, N. Y., May 31-June 1, 1955.

*brand of prednisolone

PFIZER LABORATORIES *Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York*

Enriched Bread...

and the Capacity to Work and Enjoy Life

NUTRITION EDUCATION, as important as it is, perforce is slow in effecting public health gains; practical measures on a national scale, on the other hand, can effect such gains quickly.[1] An outstanding example of practical measures for helping to overcome malnutrition has been the broad commercial enrichment of white bread initiated in 1941.

By enrichment according to official regulations, white bread became an important food for supplying thiamine, riboflavin, niacin, and iron to the national dietary.[2] Supplementing enrichment in these nutrients, nonfat milk solids are added in amounts averaging 4 per cent (by weight) of the flour component.[3] Such enriched bread is valuable not only for its contained B vitamins and iron, but for its calcium[4] and its good quality protein[5] as well.

Mortality and morbidity of nutritional deficiency diseases have dropped markedly since the advent of commercial enriched bread. No stronger evidence can be cited than the virtual elimination of pellagra in our population in recent years.[1] In 1937, pellagra mortality was 2.5 per 100,000. By 1951 it had dropped to 0.1, representing an unprecedented low of 208 deaths reported in the entire country.

But a fall in mortality data reflects only in small measure the true improvement in public health resulting from the nutritional betterment of the national dietary.[1] Of greater concern is the vast number of people who, as a result, enjoy better health with increased capacity to work and enjoy life.

1. Sebrell, W. H.: Developing Modern Nutrition Programs, Public Health Reports, United States Department of Health, Education, and Welfare *69*:277 (Mar.) 1954.
2. Jolliffe, N.: The Pathogenesis of Deficiency Disease, in Jolliffe, N.; Tisdall, F. F., and Cannon, P. R.: Clinical Nutrition, New York, Paul B. Hoeber, Inc., 1950, p. 22.
3. Cook, H. L., and Halvorson, H.: Industrial Uses and Preferences for Nonfat Dry Milk Solids, Wisconsin Agricultural Experiment Station and United States Department of Agriculture, Research Bull. 169, 1950.
4. Goddard, V. R., and Marshall, M. W.: The Calcium Content of Commercial White Bread, United States Department of Agriculture, Technical Bull. 1055, 1952.
5. Sherman, H. C.: Chemistry of Food and Nutrition, ed. 8, New York, The Macmillan Co., 1952, pp. 212, 599.

The nutritional statements made in this advertisement have been reviewed and found consistent with current medical opinion by the Council on Foods and Nutrition of the American Medical Association.

AMERICAN BAKERS ASSOCIATION
20 NORTH WACKER DRIVE • CHICAGO 6, ILLINOIS

highly potent
anti-allergic
hormone

Sterane*

in Bronchial Asthma

for rapid increase of vital capacity

3 to 5 times more potent than hydrocortisone or cortisone

notably free of major hormonal side effects such as edema due to sodium and water retention, hypopotassemia, and hypertension

seldom requires low-sodium diets or potassium supplements in patients without cardiac complications when given in usual therapeutic dosage

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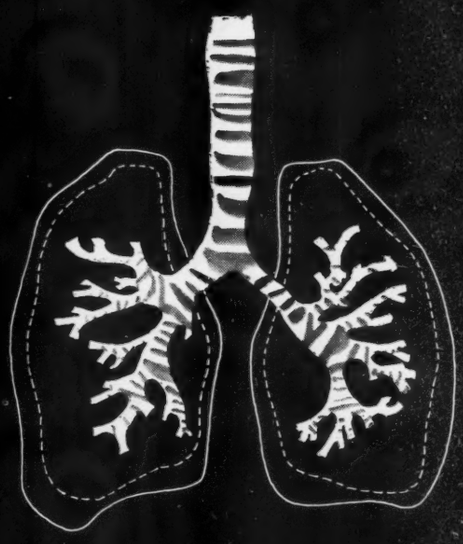


1. Forsham, P. H., et al.: Paper presented at First Internat. Conf. on Prednisone and Prednisolone, New York, N. Y., May 31-June 1, 1955.

supplied: in white, scored 5 mg. tablets in the familiar Pfizer oval shape

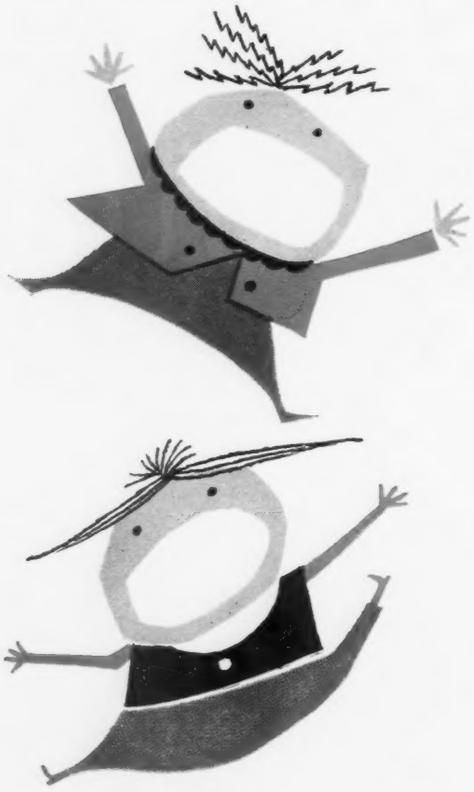
*brand of prednisolone

PFIZER LABORATORIES *Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York*

Diatussin changes difficult-to-dose children into willing patients. Mothers, too, like *Diatussin* because it's easier to give. Two to four drops do the work of spoonfuls of syrup.

Dropped directly on the tongue or on a spoonful of dessert or cereal, *Diatussin* lessens frequency and severity of cough. Non-narcotic, *Diatussin* preserves the vital cough reflex, avoids sedation and gastro-intestinal disturbances.

tykes don't "take on" when they take...



DIATUSSIN®

non-narcotic cough control

Bischoff DIVISION

Dosage:

Under 5 years...2 to 4 drops three or four times daily. Over 5 years...5 drops three or four times daily.

Formula:	*Diatussin*
Thyme (alcoholic extract) . . .	39%
Drosera (alcoholic extract) . . .	39%
Ethyl alcohol	22%

Supplied in 6-cc. bottles with dropper.

Diatussin Syrup, in 4-oz., pint and gallon bottles, contains in each teaspoonful 2 drops of the extract in an aqueous dextrose vehicle.

AMES COMPANY, INC • ELKHART, INDIANA

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reduces swelling
and inflammation
in
Allergic
and other
Dermatoses

the most potent anti-inflammatory hormone

Sterane*

3 to 5 times more potent than hydrocortisone or cortisone

notably free of major hormonal side effects such as edema due to sodium and water retention, hypopotassemia, and hypertension

seldom requires low-sodium diets or potassium supplements in patients without cardiac complications when given in usual therapeutic dosage

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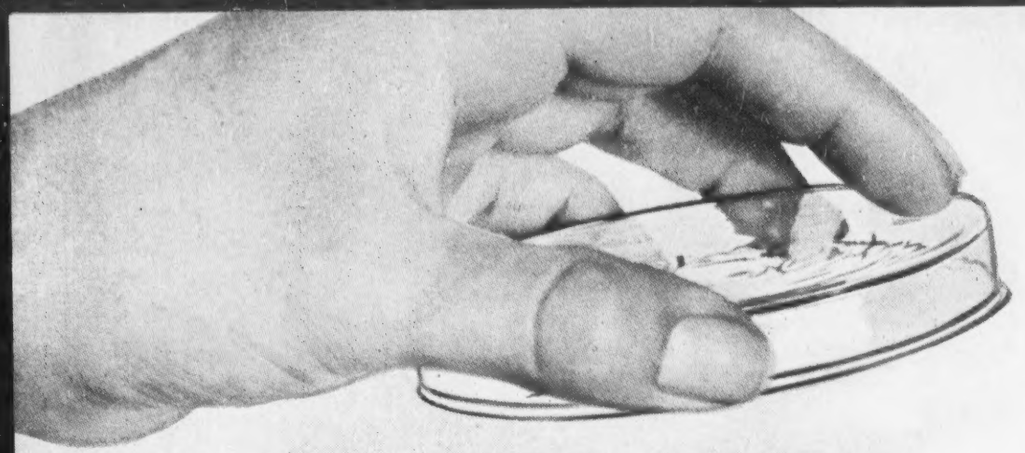
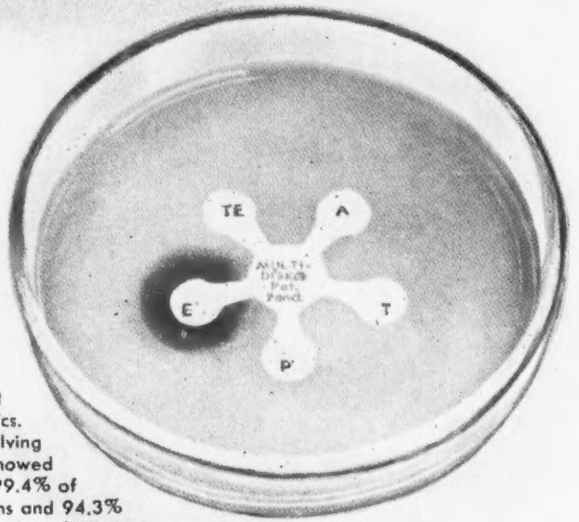




DESTROYS ENTEROCOCCI

This blood agar plate shows a strain of *beta* hemolytic enterococcus. Note extreme sensitivity of this organism to ERYTHROCIN—yet it easily resists the other antibiotics. Additional data: A study[1] involving 202 enterococcic strains showed sensitivity to erythromycin in 99.4% of *alpha* hemolytic strains and 94.3% of *beta* hemolytic strains.

specific against coccic infections

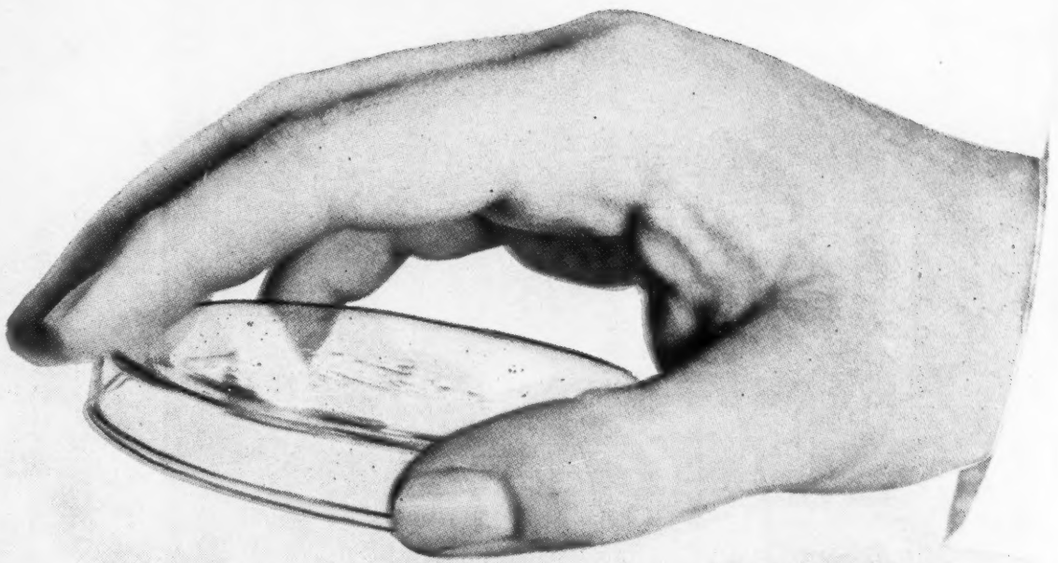
Now, you can prescribe *specific therapy* against staph-, strep- or pneumococci by simply writing *Filmtab* ERYTHROCIN Stearate. Since this coccic group causes most bacterial respiratory infections (and since these organisms are the very ones most sensitive to ERYTHROCIN) doesn't it make good sense to prescribe *Filmtab* ERYTHROCIN when the infection is coccic?

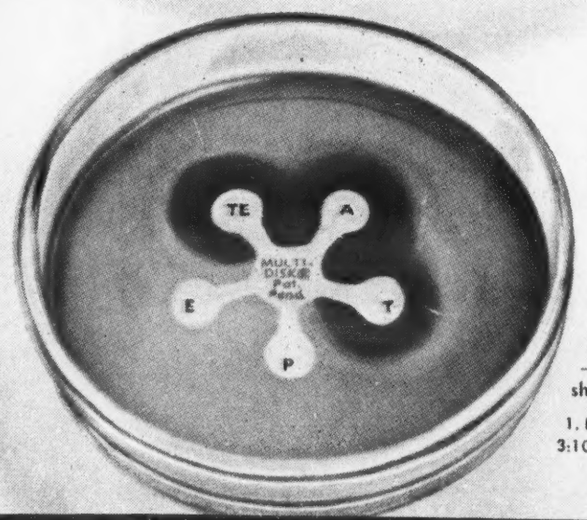
filmtab®

Erythrocin®

(Erythromycin Stearate, Abbott)

STEARATE





SPARES

INTESTINAL FLORA

This sensitivity test shows ERYTHROCIN and the same antibiotics against a typical intestinal strain of *E. coli*. Note that ERYTHROCIN and penicillin do not affect this gram-negative organism —although the other antibiotics show marked inhibitory action.

1. Eisenberg, et al., Antib. & Chemo., 3:1026-1028, Oct., 1953.

with little risk of serious side effects

Since ERYTHROCIN is inactive against gram-negative organisms, it is less likely to alter intestinal flora—with an accompanying low incidence of side effects. Also, your patients seldom get the allergic reactions sometimes seen with penicillin. Or loss of accessory vitamins during ERYTHROCIN therapy. *Filmtab* ERYTHROCIN Stearate (100 and 250 mg.) is supplied in bottles of 25 and 100 at pharmacies everywhere. Abbott

filmtab®

Erythrocin®

(Erythromycin Stearate, Abbott)

STEARATE

® Filmtab—Film scaled tablets; patent applied for.

first in advances...

first in advantages...

digitaline nativelle®

first digitalis glycoside isolated (digitoxin)

first in world usage and favorable clinical reports

first with intravenous form and pediatric oral liquid

first color-coded tablets to avoid dosage error

first digitalis glycoside with specific intramuscular form—avoids irritation often encountered when intravenous preparations are administered intramuscularly

first with a complete range of interchangeable dosage forms to meet the patient's changing needs

Consult your Physicians' Desk Reference for dosage information.

Originators of the Cardiology Desk-Aid Series.
Send for complimentary set.

VARICK PHARMACAL COMPANY, INC.
(Division of E. Fougera & Co., Inc.)
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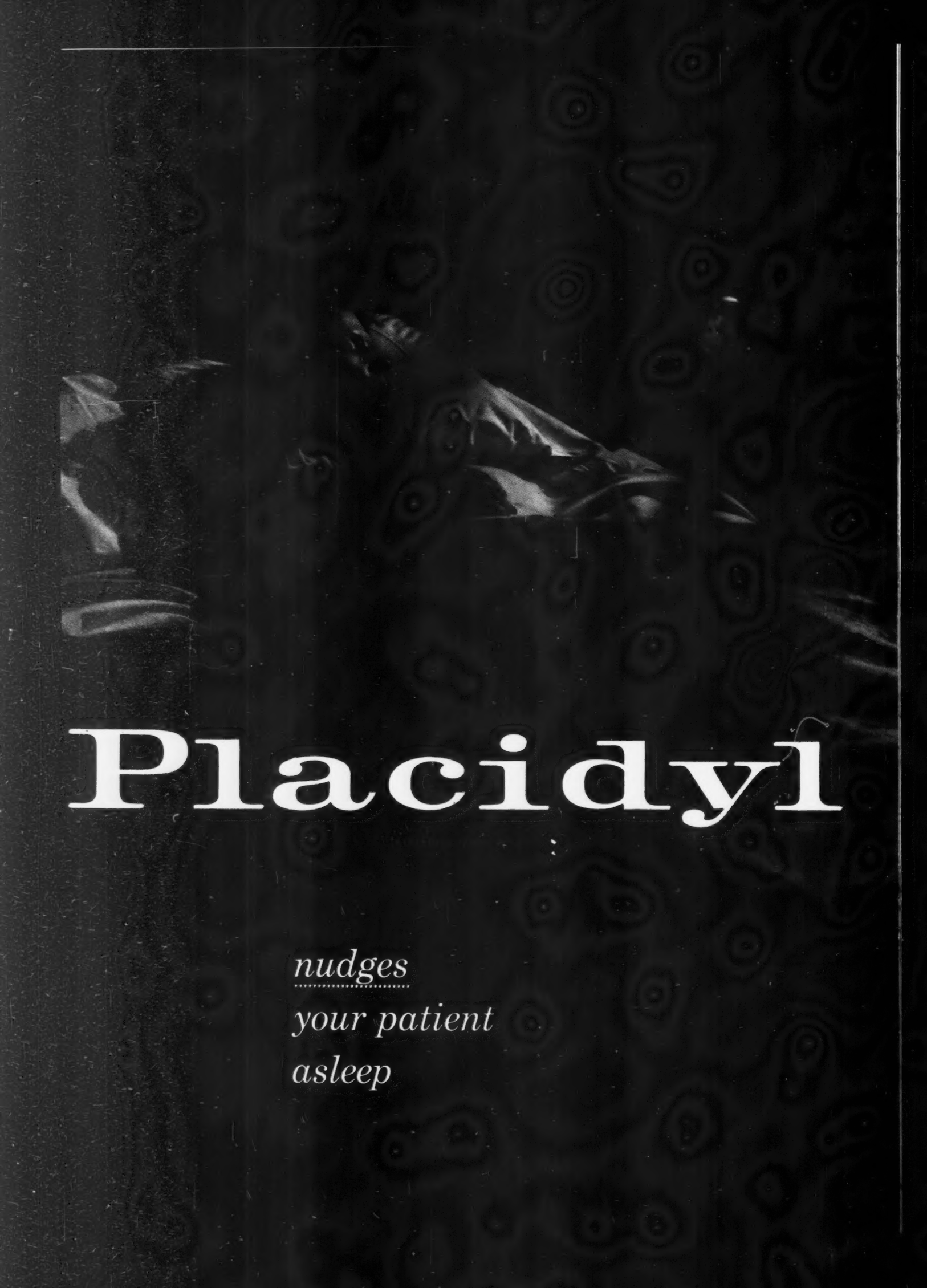
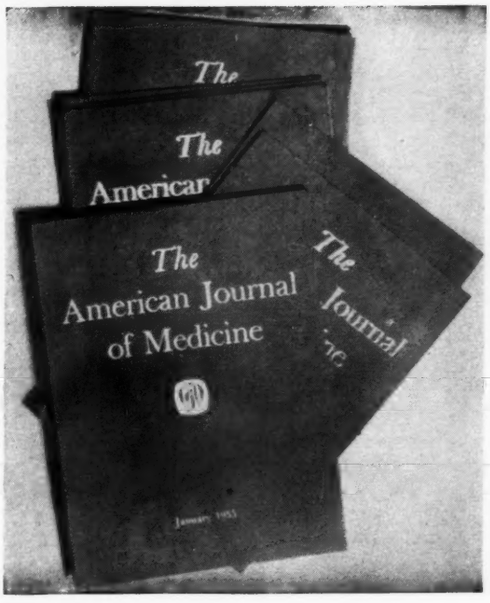

Placidyl
nudges
your patient
asleep



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More Accurate than Sedimentation Rate Determinations[1]

"False positives" do not occur in tests for C-reactive protein because this abnormal protein appears only in patients with inflammatory conditions but is never present in normal serum.[2] Disappearance of CRP or changes in its concentration parallel more closely and more promptly variations in the patient's condition than usually evidenced by fluctuations in sedimentation rate.

●

C·R·P·A

More Easily Interpreted than Sedimentation Rate Determinations[3]

There is no "normal," therefore no equivocal zone of values in the interpretation of tests for C-reactive protein.[4] CRP tests are not invalidated in patients with congestion of the liver, in heart failure, anemia, cyesis, nephrotic syndrome, or changes in fibrinogen, serum albumen or globulin, when sedimentation rates may be misleading.

●

C·R·P·A

More Convenient to Perform than Sedimentation Rate Determinations[5]

The test for C-reactive protein may be performed at any time after obtaining a sample of the patient's serum. Since a large volume of serum is not necessary, blood may be drawn from a fingertip rather than from a vein. The simple technique employed in CRP determinations facilitates *routine* use in office and hospital.

C·R·P·A®

C-reactive Protein Antiserum (Schieffelin)

For complete descriptive brochure on techniques and materials required, send request to:

Schieffelin & Co. New York 3, N. Y. • Pharmaceutical and Research Laboratories since 1794

1. Shackman, N. H., Heffer, E. T., and Kroop, I. G.: Am. Heart J. 48:599 (Oct.) 1954. • 2. Stollerman, G. H., and others: Am. J. Med. 15:645 (Nov.) 1953. • 3. McEwen, C.: M. Clin. North America 39:353 (March) 1955. • 4. Wood, H. F., and McCarty, M.: Am. J. Med. 17:768 (Dec.) 1954. • 5. McEwen, C., and Ziff, M.: M. Clin. North America (May) 1955, to be published.

SALINE SUSPENSION

HydroCortone®-T.B.A.

(HYDROCORTISONE *TERTIARY*-BUTYLACETATE. MERCK)

NEW longer-acting hydrocortisone ester provides prolonged relief for painful joints

MAJOR ADVANTAGES: Pronounced and prolonged local anti-inflammatory effect. Longer, more intense action than with hydrocortisone acetate.

HYDROCORTONE-T. B. A. is a very slightly soluble ester of hydrocortisone. Comparable dosage of this new ester produces a longer and more intense local anti-inflammatory effect than hydrocortisone acetate when injected into the synovial spaces. The duration of relief may be from two to ten times longer.

Saline Suspension HYDROCORTONE-T. B. A. is particularly advantageous in the treatment of patients with rheumatoid arthritis or osteoarthritis. While severely inflamed joints may require one or more injections a week, the milder cases may show benefit for as long as 8 or 9 weeks.

Since the anti-inflammatory action is entirely local, HYDROCORTONE-T. B. A. may be used in conjunction with systemic steroid therapy as well as in those patients in whom systemic therapy is contraindicated.

SUPPLIED: Saline Suspension HYDROCORTONE-T. B. A.:25 mg./cc., vials of 5 cc.; Saline Suspension HYDROCORTONE Acetate: 25 mg./cc., vials of 5 cc. ORAL—HYDROCORTONE Tablets: 20 mg., bottles of 25, 100, and 500 tablets; 10 mg., bottles of 50, 100, and 500 tablets; 5 mg., bottles of 50 tablets.

SHARP & DOHME

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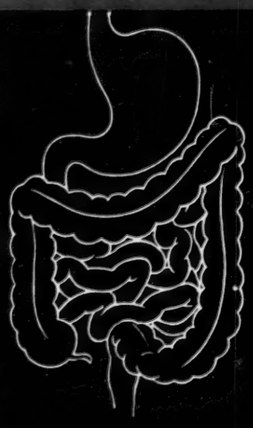

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HYDROGEN SULFATE

is the most potent synthetic antispasmodic agent available for gastrointestinal therapy

Laboratory experiments show that Centrine is more effective than atropine in controlling gastrointestinal hypermotility[1]—as manifest by superior reduction in the number, tone, amplitude and duration of peristaltic contractions; and it successfully relieves localized spasm.[cf.2] It is 5 to 100 times more potent than other synthetic antispasmodic agents commonly used.

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References: 1. J. Pharm. & Exp. Ther., 98:14, 1950.
2. Gastroenterology, 24:204, 1953.

BRISTOL LABORATORIES INC.
SYRACUSE, NEW YORK

Available for your prescription as:
Centrine Tablets (0.5 mg.)
Centrine Tablets with Phenobarbital
(0.5 mg., with 15.0 mg. (¼ gr.) phenobarbital)
Centrine Solution (0.5 mg. per 10 drops)

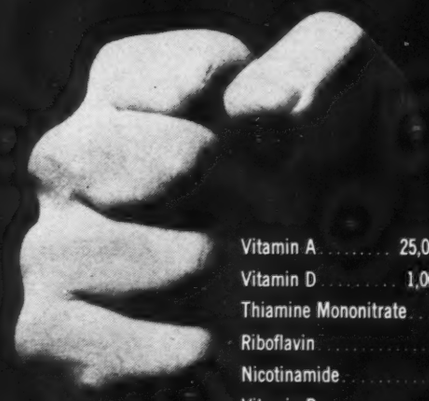
the only

THERAPEUTIC FORMULA

multivitamin tablet . . .

this small . . .

this potent . . .



Vitamin A	25,000 units (7.5 mg.)
Vitamin D	1,000 units (25 mcg.)
Thiamine Mononitrate	10 mg.
Riboflavin	5 mg.
Nicotinamide	150 mg.
Vitamin B_{12}	6 mcg.
Ascorbic Acid	150 mg.

and this pleasing . . .

(A solid tablet – not a soft, sticky capsule. Pleasant-tasting – no fish-oil odor, taste, burp or allergies.)

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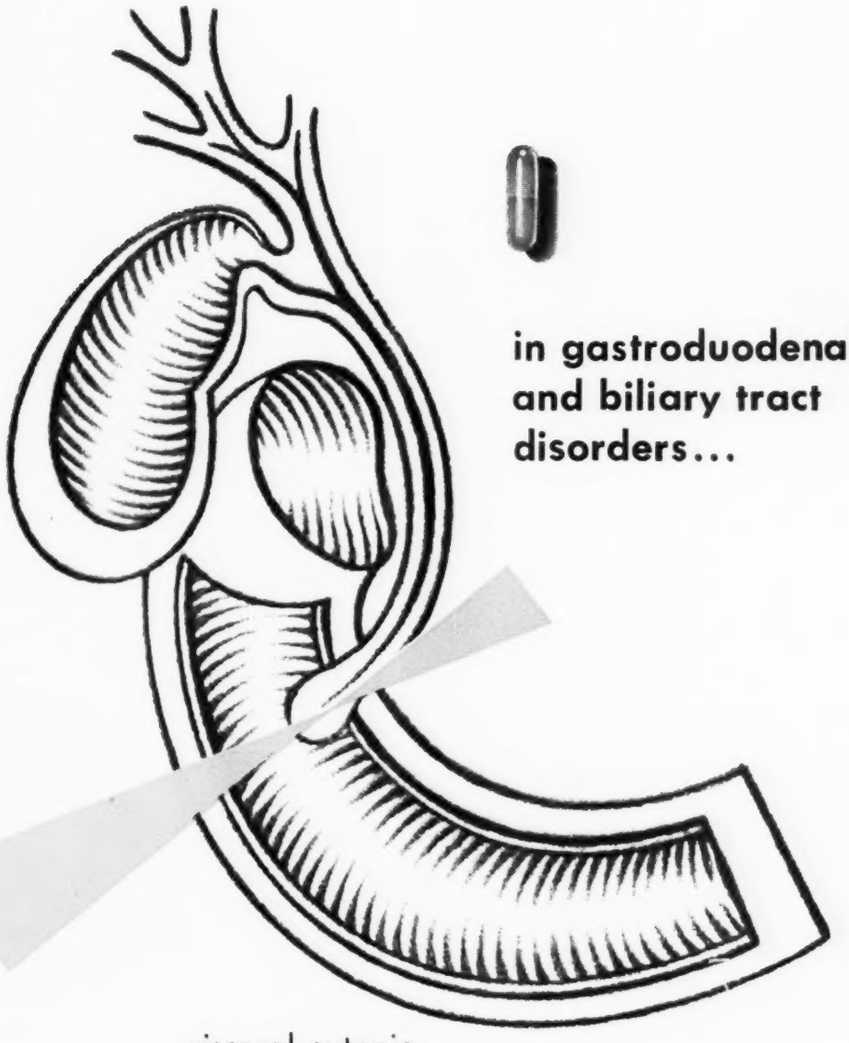

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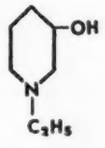
PLAIN AND WITH PHENOBARBITAL

relieves **pain ⇄ spasm** *usually in 10 minutes*

prompt action at the site of visceral pain gives unusually rapid relief

prolonged control of spasm gives relief up to four hours

no interference with digestive secretions, normal tonus or motility



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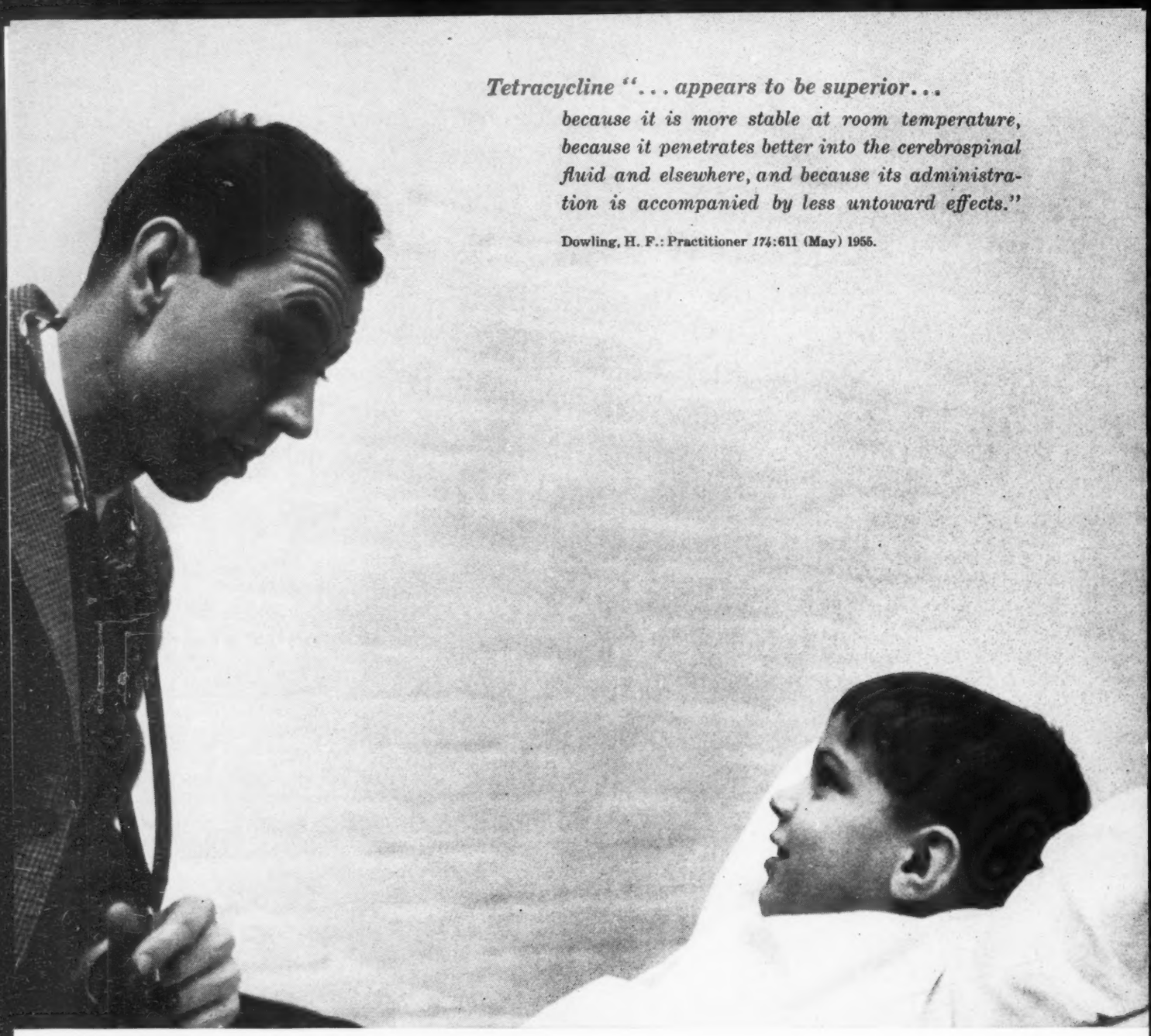

Tetracycline "... appears to be superior...
because it is more stable at room temperature, because it penetrates better into the cerebrospinal fluid and elsewhere, and because its administration is accompanied by less untoward effects."

Dowling, H. F.: Practitioner *174*:611 (May) 1955.

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the original tetracycline

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Tablets and Capsules, 50, 100 and 250 mg.,
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"Complete to Excellent Control" of Seizures was Achieved with "Mysoline" in More than 50 per cent of Patients Previously Uncontrolled with Other Anticonvulsants.

Timberlake, Abbott, and Schwab* report "100 per cent control" with "Mysoline" in 22 patients and from "50 to 100 per cent control" in another 28, in a series of 96 patients with grand mal and psychomotor seizures.

Grand mal seizures were completely eliminated in 14 of 38 patients (4 receiving "Mysoline" alone), and in 9 the frequency of seizures was reduced by more than half. Two patients in *status epilepticus* were also brought under control with "Mysoline."

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In general, "Mysoline" was well tolerated. No side effects occurred in 34 per cent of the patients. In other cases, side effects such as drowsiness, dizziness, and ataxia were frequently noted at the start of therapy but tended to disappear as therapy was continued.

To minimize side effects, these workers recommend small initial doses of "Mysoline," 0.125 Gm. (half tablet) daily, to be increased by 0.125 Gm. increments at three to seven day intervals.

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"Mysoline" is supplied in 0.25 Gm. tablets (scored), bottles of 100 and 1,000.

*Timberlake, W. H., Abbott, J. A., and Schwab, R. S.: New England J. Med. *252*:304 (Feb. 24) 1955.

"MYSOLINE"®

Brand of Primidone

in epilepsy

Ayerst Laboratories • New York, N. Y. • Montreal, Canada

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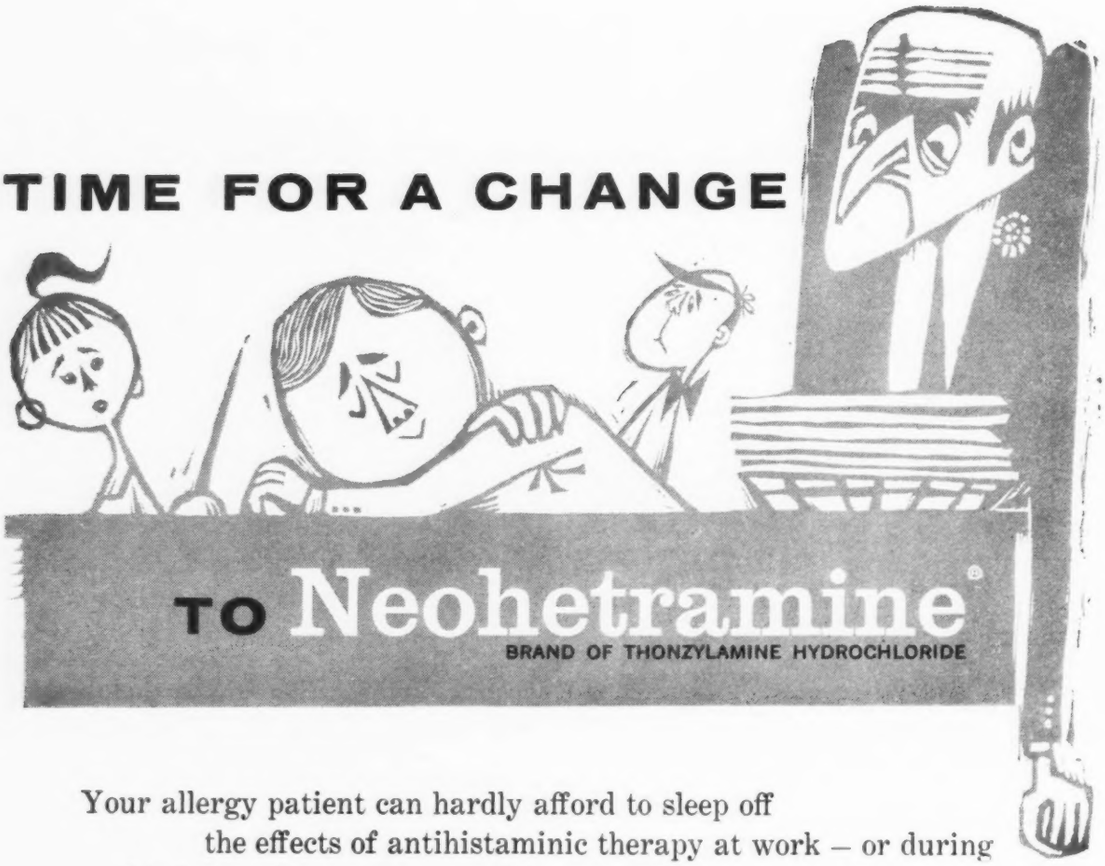

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BRAND OF THONZYLAMINE HYDROCHLORIDE

Your allergy patient can hardly afford to sleep off the effects of antihistaminic therapy at work – or during his leisure hours. To spare him this dilemma, prescribe . . .

Neohetramine® *the effective antihistaminic that does not impair normal daytime alertness.*

Neohetramine is virtually free from sedation.

Neohetramine is extremely well tolerated.

Neohetramine is particularly useful in pediatric practice because of its markedly lower incidence of side reactions.

Dosage: Initiate with 50 mg. tablets or syrup, two to four times daily for adults, 25 mg. two to four times daily for children, and increase according to individual response.

Supplied: *Tablets* — 25 mg., 50 mg., and 100 mg. *Syrup* — 25 mg. per teaspoonful (4 cc.) *For topical application:* Cream 2% in one ounce tubes.

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NEPERA

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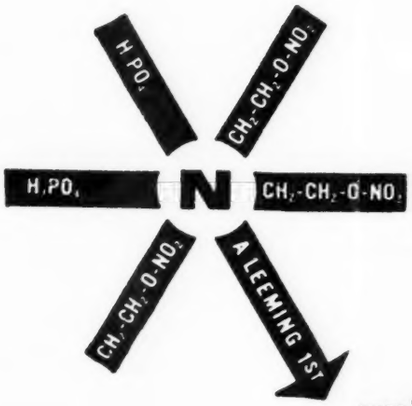
Angina pectoris prevention



Most efficient of the new long-acting nitrates, METAMINE prevents angina attacks or greatly reduces their number and severity. Tolerance and methemoglobinemia have not been observed with METAMINE, nor have the common nitrate side effects such as headache or gastric irritation. Dose: 1 or 2 tablets after each meal and at bedtime. Also: METAMINE (2 mg.) with BUTABARBITAL (¼ gr.), bottles of 50. THOS. LEEMING & CO., INC., 155 EAST 44TH STREET, NEW YORK 17, N.Y.

unique amino nitrate

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triethanolamine trinitrate biphosphate, Leeming, tablets 2 mg. Bottles of 50 and 500

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A well-balanced, high-potency vitamin formula containing B-Complex and C

FOLBESYN provides B-Complex factors (including folic acid and B_{12}) and ascorbic acid in a well balanced formula. It does not contain excessive amounts of any one factor.

FOLBESYN Parenteral may be administered intramuscularly, or it may be added to various hospital intravenous solutions. It is useful for preoperative and postoperative treatment and during convalescence.

Dosage: 2 cc. daily. Each 2 cc. provides:

Thiamine HCl (B_1)	10 mg.
Sodium Pantothenate	10 mg.
Niacinamide	50 mg.
Riboflavin (B_2)	10 mg.
Pyridoxine HCl (B_6)	5 mg.
Ascorbic Acid (C)	300 mg.
Vitamin B_{12}	15 micrograms
Folic Acid	3 mg.

FOLBESYN is also available in tablet form, ideal for supplementing the parenteral dose.

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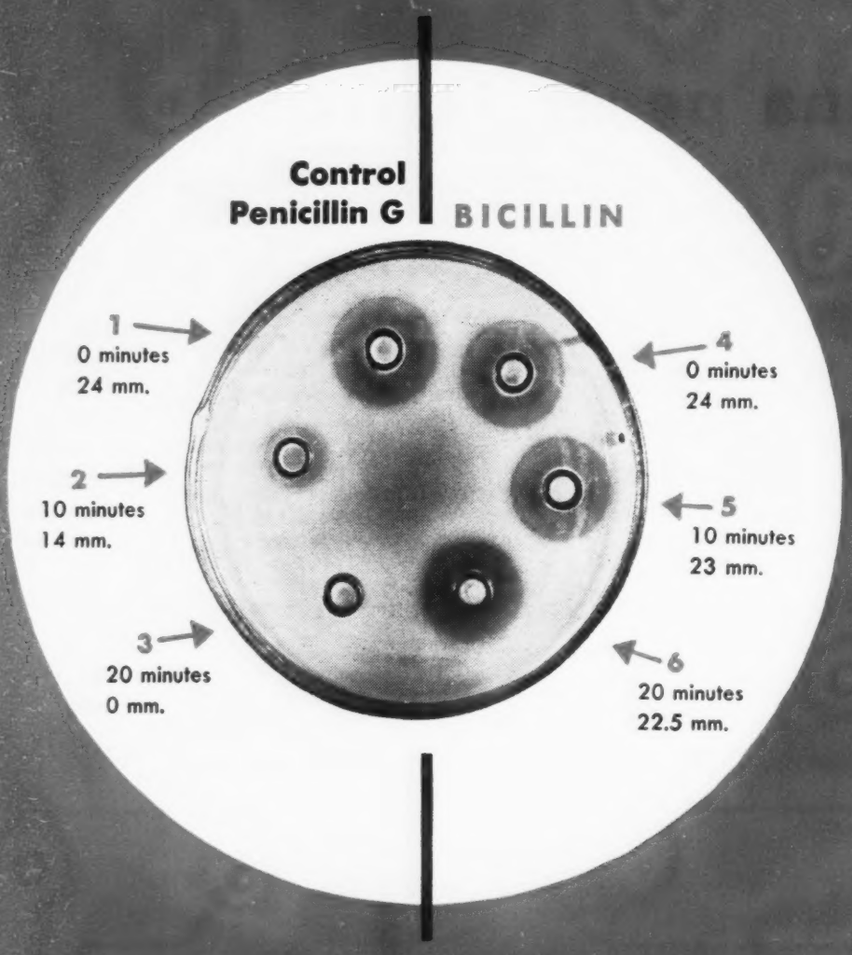

Comparing antibacterial potency of two unbuffered penicillins. Zones of inhibition of Staphylococcus aureus, strain 209 P.

Protected Penicillin
means
Systemic Penicillin

Oral BICILLIN is *self-protected* penicillin because it protects itself against gastric destruction. This unique quality is the result of a molecular structure that gives Oral BICILLIN high durability in gastric acid,[1] effectively guarding the penicillin for its antibacterial role. Administer without regard to meals.

1. American Medical Association: New and Nonofficial Remedies. J. B. Lippincott Co., Philadelphia, 1954, p. 147.

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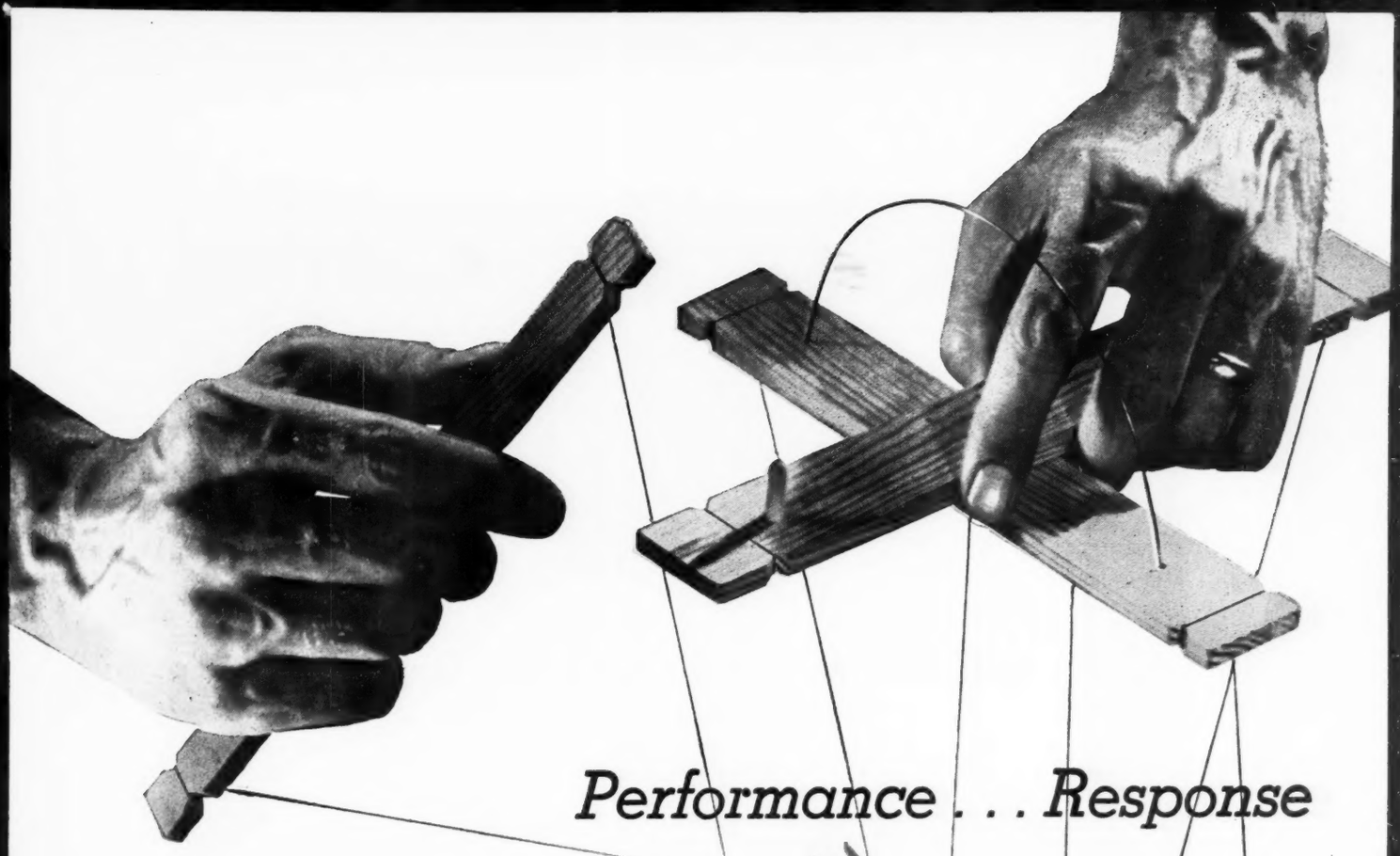
Benzathine Penicillin G (Dibenzylethylenediamine Dipenicillin G)

Penicillin with a Surety Factor



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Salcort performance stimulates a dependable response in arthritic conditions; early functional improvement and a sense of well being are significant. Smaller doses of salicylates and cortisone combined produce a therapeutic response equivalent to that of large doses of cortisone . . . side reactions are eliminated and continuous therapy is permitted. Salcort presents no withdrawal problems.

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Cortisone Acetate	2.5 mg.
Sodium Salicylate	0.3 Gm.
Aluminum Hydroxide Gel, dried	0.12 Gm.
Calcium Ascorbate	60 mg.
(equivalent to 50 mg. Ascorbic Acid)	
Calcium Carbonate	60 mg.

*U. S. Patent No. 2691662

professional literature and sample available on request

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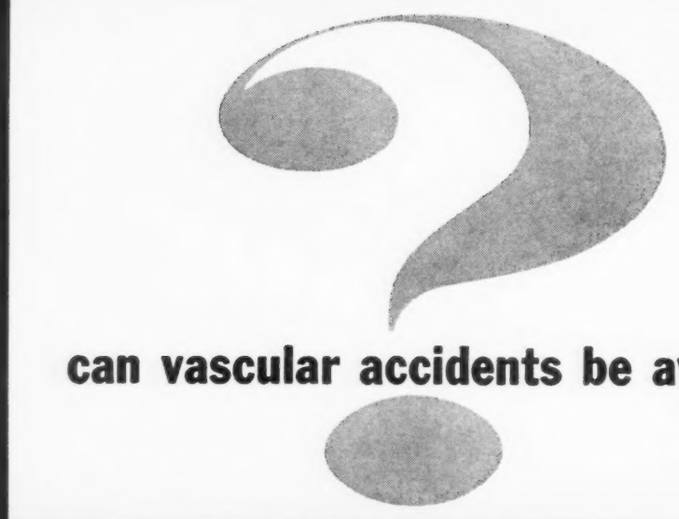

can vascular accidents be avoided

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helps diminish abnormal capillary permeability and fragility in hypertension, diabetes, atherosclerosis and other cardiovascular conditions

C.V.P. acts to maintain the integrity of the intercellular cement substance of capillary walls and so aids in increasing capillary resistance, overcoming abnormal capillary fragility, checking capillary hemorrhage . . . and thus may help protect against vascular accidents in patients with capillary fault.

C.V.P. provides natural water-soluble bioflavonoid compound (sometimes referred to as "vitamin P complex") derived from citrus sources, combined with ascorbic acid. It is believed to be more readily absorbed than relatively insoluble rutin. C.V.P. is safe . . . exceptionally well-tolerated.

Each C.V.P. capsule or teaspoonful (5 cc.) of syrup provides:

Citrus Flavonoid Compound . . .	100 mg.
Ascorbic Acid (vitamin C)	100 mg.

Bottles of 50, 100, 500 and 1000 capsules; 4 oz., 16 oz. and gallon syrup.

samples (capsules or syrup) and literature from . . .

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safely

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(dextro-amphetamine plus minerals and vitamins, Roerig)

each AM-PLUS capsule contains:

Dextro Amphetamine Sulfate U.S.P.	5 mg.
Vitamin A (Palmitate)	5,000 U.S.P. Units
Vitamin D (Irradiated Ergosterol)	400 U.S.P. Units
Thiamine HCl U.S.P.	2 mg.
Riboflavin U.S.P.	2 mg.
Pyridoxine HCl U.S.P.	0.5 mg.
Niacinamide U.S.P.	20 mg.
Ascorbic Acid U.S.P.	37.5 mg.
Calcium Pantothenate	3 mg.
Calcium (from Dicalcium Phosphate)	242 mg.
Cobalt (from Cobaltous Sulfate)	0.1 mg.
Copper (from Cupric Sulfate)	1 mg.
Iodine (from Potassium Iodide)	0.15 mg.
Iron (from Ferrous Sulfate)	3.33 mg.
Manganese (from Manganous Sulfate)	0.33 mg.
Molybdenum (from Sodium Molybdate)	0.2 mg.
Magnesium (from Magnesium Sulfate)	2 mg.
Phosphorus (from Dicalcium Phosphate)	187 mg.
Potassium (from Potassium Sulfate)	1.7 mg.
Zinc (from Zinc Sulfate)	0.4 mg.

dosage: Two or three capsules daily, one-half hour before meals.

In bottles of 100 soft, soluble capsules.

1. MacBryde, C. M.: in Current Therapy, W. B. Saunders Co., Philadelphia, 1953, p. 350.

Adequate minerals and vitamins must be supplied in any long-continued weight reducing program.[1]

AM-PLUS: Supplies 11 important minerals and 8 essential vitamins **and** decreases appetite and elevates mood—safely—with dextro-amphetamine.

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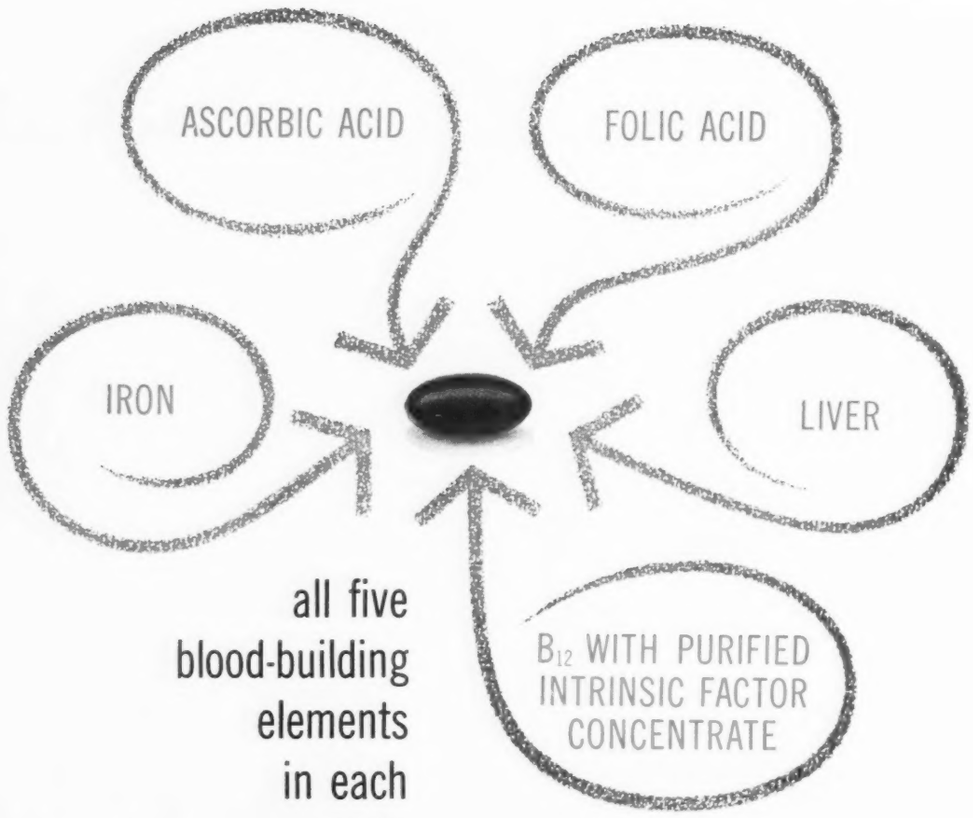

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PERIHEMIN builds blood!

Available in Capsules and JR Capsules for children.

Recommended dosage: 1 capsule t.i.d.

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Vitamin B_{12} (additional)	5 mcgm.
Ferrous Sulfate (exsiccated)	192 mg.
Folic Acid	0.85 mg.
Ascorbic Acid (C)	50 mg.
Insoluble Liver Fraction	50 mg.

JR Capsules are approximately one-quarter the potency of this formula.

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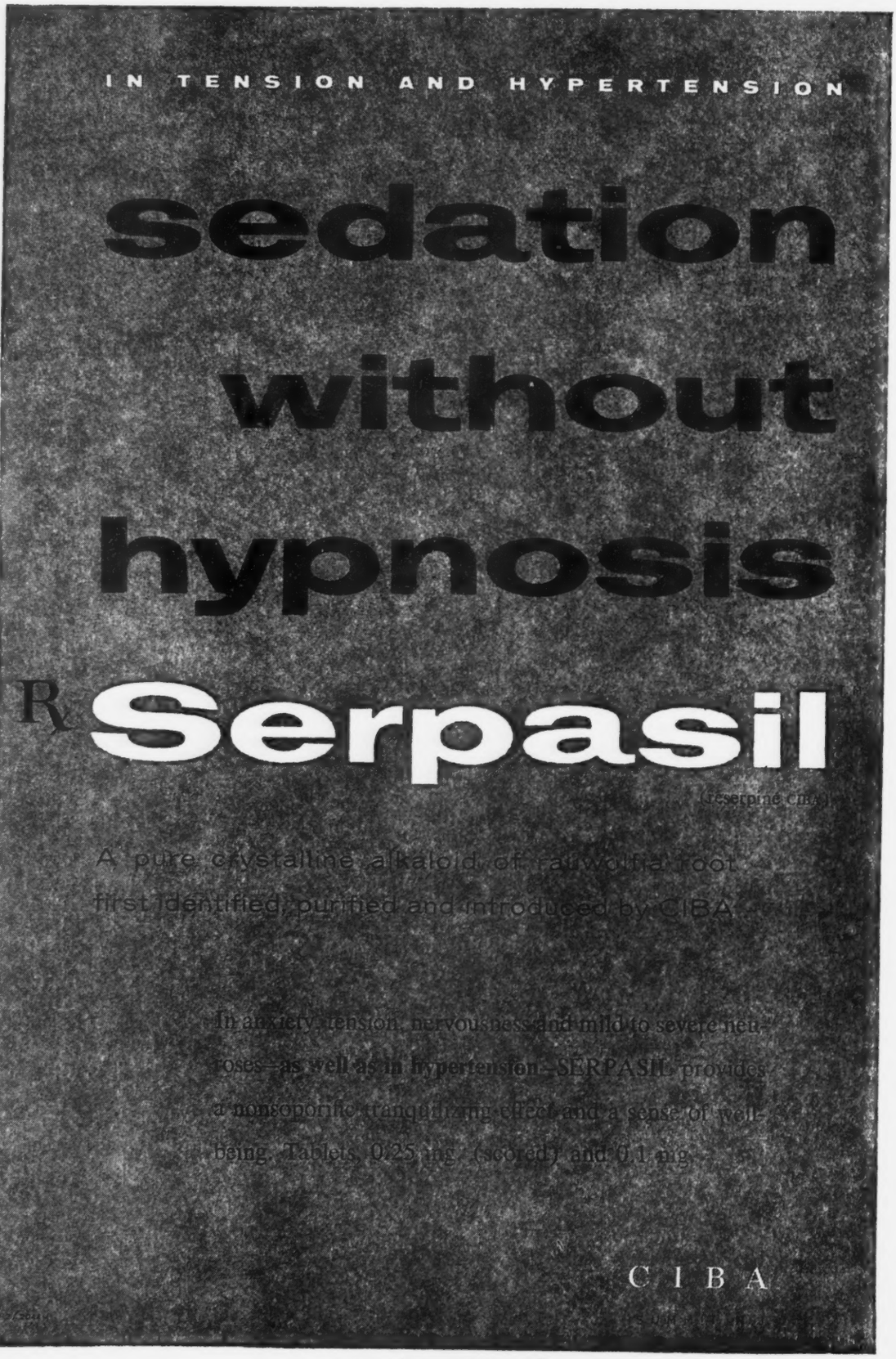
October, 1955



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